Control of Cardiac Output in Thyrotoxic Calves

Evaluation of Changes in the Systemic Circulation

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Abstract. The contribution of peripheral vascular factors to the high output state in thyrotoxicosis was examined in 11 calves treated with daily intramuscular injections of L-thyroxine (200 μg/kg) for 12–14 d. Thyroxine treatment increased cardiac output from 14.1±1.4 to 24.7±1.4 liters/min ($P < 0.001$) and decreased systemic vascular resistance from 562±65 to 386±30 dyn-s/cm^5 ($P < 0.01$). Blood volume was increased from 65±4 ml/kg in the euthyroid state to 81±6 ml/kg when the animals were thyrotoxic ($P < 0.05$). The role of low peripheral vascular resistance in maintenance of the high output state was evaluated by infusion of phenylephrine at two dosages (2.5 and 4.0 μg/kg per min). In the euthyroid state, no significant decrease in cardiac output was observed at either level of pressor infusion. In the thyrotoxic state, the higher dosage of phenylephrine increased peripheral resistance to the euthyroid control level and caused a small (6%) decrease in cardiac output ($P < 0.05$). This small decrease in cardiac output probably could be attributed to the marked increase in left ventricular afterload caused by the pressor infusion as assessed from measurements of intraventricular pressure and dimensions. Changes in the venous circulation were evaluated by measurement of mean circulatory filling pressure and the pressure gradient for venous return in six animals during cardiac arrest induced by injection of acetylcholine into the pulmonary artery. Mean circulatory filling pressure increased from 10±1 mmHg in the euthyroid state to 16±2 mmHg ($P < 0.01$) during thyrotoxicosis, while pressure gradient for venous return increased from 10±1 to 14±2 mmHg ($P < 0.02$). These changes in venous return curves were not affected significantly by ganglionic blockade with trimethapan (2.0 mg/kg per min) before cardiac arrest. Thus, the high output state associated with thyrotoxicosis is not dependent upon a low systemic vascular resistance, but is associated with increases in blood volume, mean circulatory filling pressure, and pressure gradient for venous return.

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Introduction

The cardiac output is often increased two to three times in thyrotoxic subjects (1) and in animals (2, 3) treated with exogenous thyroid hormone. A variety of mechanisms have been postulated to explain the augmentation in cardiac output, including chronotropic and inotropic stimulation of the heart, increased blood volume, and decreased systemic arterial resistance (4). However, recent experiments and analyses suggest that none of these factors are likely to account for an increase in cardiac output of this magnitude. For instance, an increase in heart rate induced by electrical pacing fails to increase the resting cardiac output by more than a few percent (5). Also, a chronic increase in blood volume causes hardly any increase in cardiac output, but rather, usually causes an increase in arterial pressure (6, 7).

Beginning with Guyton and co-workers (8), the importance of venous factors in the regulation of cardiac output have been recognized. Their studies demonstrated that the pressure difference between the peripheral veins and right atrium, the so-called pressure gradient for venous return (PGVR),[1] is a major determinant of blood flow returning to the heart. When this concept is combined with the classical formulation for control of cardiac output as a function of right atrial (RA) pressure and

1. *Abbreviations used in this paper:* LA, left atrial; LV, left ventricular; MCFP, mean circulatory filling pressure; PGVR, pressure gradient for venous return; RISA, radioactive ^{131}I-serum albumin.

inotropic state, that is, as a family of ventricular function (Frank-Starling) curves, a framework is provided for evaluating the relative importance of changes in the heart and peripheral circulation in alterated hemodynamic states.

In the present study, we have examined the effects of excess thyroid hormone on the systemic circulation in conscious calves, some of which were instrumented with sonomicrometer crystals and pressure catheters to permit simultaneous evaluation of left ventricular (LV) performance. The effects on cardiac output produced by normalizing the systemic vascular resistance with phenylephrine, a relatively pure alpha-adrenergic agonist, were determined before and after treatment with thyroid hormone. In addition, changes in the venous return curve were monitored by measuring the systemic venous pressure during acetylcholine-induced cardiac arrest, that is, the mean circulatory filling pressure (MCFP). The results indicate that the high output state in thyrotoxicosis is not dependent upon maintenance of a low systemic vascular resistance, but may result from a shift in the venous return curve such that the new curve crosses the new cardiac function curve at a higher intercept on the flow axis, resulting in a marked increase in cardiac output.

Methods

Animal experiments. Experiments were performed on 11 calves about 5–6 mo of age (90–130 kg). In six animals, sonomicrometer crystals and pressure transducers were implanted into the LV by using the operative techniques described earlier (3). A high fidelity micromanometer (Konigsberg Instruments, Pasadena, CA, P-7) was inserted into the LV chamber through a stab incision in the apex of the heart. Pacing electrodes were sutured to the left atrial (LA) appendage. Two pairs of 5-MHz sonomicrometer crystals, measuring either 4 or 5 mm in diameter, were placed in the LV wall to continuously measure LV wall thickness and LV minor diameter. For LV minor diameter measurements, one crystal was placed through a diagonally directed stab wound created by a No. 16 gauge needle onto the posterior endocardial surface of the ventricle near the minor equator. The other endocardial crystal was placed slightly lateral to the left anterior descending coronary artery. The second pair of crystals was placed on either surface of the LV free wall in the same plane. This crystal pair was used for measurement of LV wall thickness. All crystals were positioned so as to provide the shortest possible ultrasonic transit time. The position of the crystals was verified at necropsy.

In six animals, aortic pressures were recorded through 3-mm silastic tubing in the right carotid artery which was connected to a P23ID strain gauge (Statham Instruments, Inc., Oxnard, CA). The gauge was positioned at the mid-chest level and referenced to atmospheric pressure. LV mechanical and hemodynamic measurements were made in the standing position without sedation. Data were recorded on an oscillographic recorder (VR-6, Electronics for Medicine, Inc., Pleasantville, NY). The sonomicrometer crystals were attached to an electronic system (Triton Technology, San Diego, CA) which has been described earlier (9). Cardiac output was measured in triplicate using a flow-directed thermal dilution pulmonary artery catheter and a minicomputer (No. 9510-A, Edwards Laboratories, Santa Ana, CA).

Control measurements of heart rate, aortic pressure, LV pressure, and wall motion were made daily from 7 to 10 d after surgery in the conscious, unsedated state with the heart beating spontaneously. When stable values had been achieved, the effects of elevation of systemic blood pressure by phenylephrine infusion on LV function and cardiac output were determined. The animals then were lightly anesthetized with a mixture of halothane, nitrous oxide, and oxygen and a control value of MCFP was obtained. Thyrotoxicosis was induced by daily intramuscular injection of L-thyroxine (200 μg/kg). All measurements were repeated 12–14 d after the initial dose of thyroxine.

Phenylephrine infusion. Phenylephrine was administered by continuous intravenous infusion at an initial rate of 2.5 μg/kg per min. This dose was sufficient to increase peak systolic blood pressure to ~175 mmHg. Heart rate was held constant by electronic atrial pacing at a value slightly greater than the sinus rate in order to insure complete capture. A small dose of atropine (0.1 mg) was used, if necessary, to maintain 1:1 atrioventricular conduction. After the blood pressure had been maintained at this level for 10 min, recordings of cardiac output, aortic pressure, and LV wall motion were made. The phenylephrine infusion rate then was increased to 4.0 μg/kg per min, which increased arterial systolic pressure to ~200 mmHg and all recordings were repeated (Fig. 1).

Measurement of MCFP. MCFP was measured in the control state and after 2 wk of thyroid hormone by the method described by Young et al. (10). Animals were lightly anesthetized with halothane, nitrous oxide, and oxygen. Acetylcholine (150 mg) was administered as a bolus injection through a percutaneously introduced pulmonary artery catheter. Aortic and RA pressures were recorded during asystole.

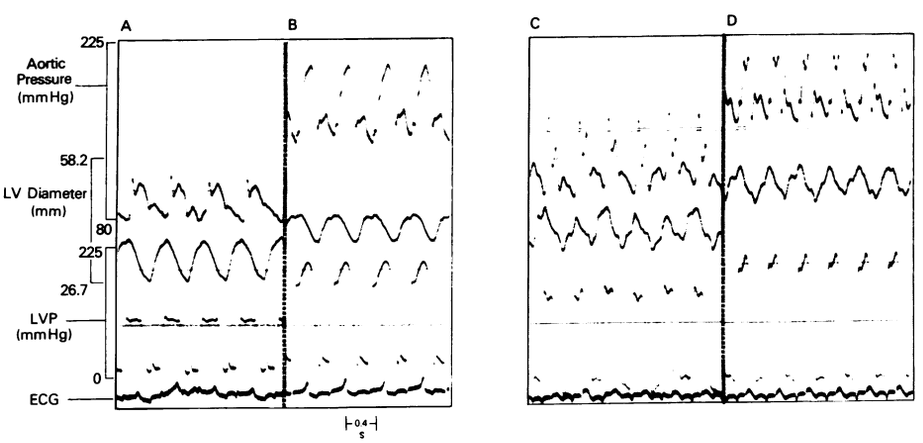

Figure 1. Recordings of electrocardiogram, LV pressure, LV diameter, and aortic pressure in a conscious euthyroid calf at rest (*A*) and during intravenous infusion of phenylephrine (4 μg/kg per min) (*B*). On the left are shown similar tracings from the same animal after 2 wk of treatment with thyroxine at rest (*C*) and during phenylephrine infusion (*D*).

Calculations. LV pressures were recorded with a Konigsberg Instruments P-7 solid state pressure transducer. The value for maximum LV dP/dt was obtained from an electronic differentiating circuit in the oscillographic recorder. Wall stress (WSt) was calculated from LV pressure (P), internal minor diameter (D), and wall thickness (WTh) as described earlier (3, 11), assuming a spherical model of the ventricle: $WSt = P \times D/(4 \times WTh)$. Measurements were made at 40-ms intervals and peak wall stress values are reported.

Total vascular resistance was calculated as given below. Systemic vascular resistance = (mean aortic pressure − mean RA pressure)/cardiac output.

MCFP was calculated from the systemic arterial and RA pressures after acetylcholine arrest as described earlier (10):

MCFP = RA pressure + [(Arterial pressure − RA pressure)/30].

The PGVR was calculated as the MCFP minus the RA pressure obtained just before cardiac arrest (10).

Blood volume determinations. Blood volumes were measured in six animals before and after thyroid administration using radioactive ^{131}I-serum albumin (RISA) according to the method described by Blahd (12).

Statistics. Statistical analysis of the significance of differences between mean values was made using the t test for paired values. Intergroup comparisons between control values and those obtained after infusion of phenylephrine were made by Dunnett's test for multiple comparisons vs. a control, after analysis of variance had demonstrated statistically significant changes.

Table I. Hemodynamic and LV Wall Motion Measurements in Euthyroid and Thyrotoxic Calves

	Euthyroid	Thyrotoxic	P Values
Heart rate (*beats/min*)	96±5	146±6	<0.01
RA pressure (*mmHg*)	1±1	1±1	NS
LV systolic pressure (*mmHg*)	114±4	148±6	<0.02
LV end-diastolic pressure (*mmHg*)	6±1	6±2	NS
LV dP/dt (*mmHg/s*)	1,454±121	2,691±307	<0.02
Systolic aortic pressure (*mmHg*)	113±4	150±5	<0.001
Diastolic aortic pressure (*mmHg*)	73±7	94±5	<0.01
Mean aortic pressure (*mmHg*)	90±4	115±3	<0.001
Cardiac output (*liters/min*)	14.1±1.4	24.7±1.4	<0.001
Stroke volume (*ml*)	150±16	174±13	NS
Systemic vascular resistance (*dyn-s/cm^5*)	563±65	386±30	<0.01
LV diastolic diameter (*mm*)	45±4	53±4	<0.05
LV systolic diameter (*mm*)	36±4	43±4	<0.05
LV wall thickness systole (*mm*)	13±2	12±2	NS
LV wall thickness diastole (*mm*)	11±2	11±2	<0.05
Peak wall stress (*10^3 dyn/cm^2*)	143±12	232±27	<0.01

Values for LV dimensions and wall stress are mean±SE for six calves; the hemodynamic data are from 11 calves.

Results

Effects of thyroxine on LV performance. Heart rate, RA pressure, aortic pressure, cardiac output, peripheral vascular resistance, and LV dimensional measurements before and after treatment with thyroxine for 12–14 d are given in Table I. Mean aortic pressure and cardiac output were significantly greater than control ($P < 0.001$) while peripheral vascular resistance was diminished. LV dP/dt was increased by ~85% compared with the euthyroid value ($P < 0.02$). LV systolic and diastolic diameters also were significantly increased ($P < 0.05$). These increases in LV dimensions corresponded to an increase in stroke volume from an average value of 150±16 ml in the euthyroid state of 174±13 ml after thyroxine treatment. Average LV wall thickness at end-diastole was somewhat less than control after treatment with thyroid hormone ($P < 0.05$). RA pressure and LV fractional shortening were unchanged in the thyrotoxic state. These base-line measurements of hemodynamics and LV mechanical function in euthyroid and thyrotoxic calves are similar to those we have reported earlier (3).

Effect of phenylephrine. The hemodynamic effects of two dose levels of phenylephrine in the euthyroid state and after 2 wk of thyroxine treatment are represented graphically in Fig. 2 to illustrate the similarities in the effects on arterial blood pressure and cardiac output in both thyroid states. Statistical analysis of the phenylephrine data is presented in Table II.

Phenylephrine produced dose-related increases in the average mean aortic pressures of both groups. The increments in pressures in the thyrotoxic state, however, were not appreciably different from those in the euthyroid state. Heart rate was held constant during these experiments by atrial pacing and atropine to prevent the reflex bradycardia that otherwise would have occurred.

Phenylephrine produced no appreciable change in cardiac output during the euthyroid state. In the thyrotoxic state, only a slight decrease in cardiac output occurred at the highest dose level. Although the incremental increases in peripheral vascular resistance were less in the thyrotoxic state, the absolute value for resistance at the highest phenylephrine dosage level exceeded that in the euthyroid control state (602±34 vs. 562±65 dyn-s-cm^5). Thus, despite normalization of systemic vascular resistance by the pressor effects of phenylephrine, cardiac output in the thyrotoxic state remained almost twice the euthyroid value.

Changes in LV end-diastolic pressure and wall motion during the phenylephrine infusions also were observed (Table II). LV end-diastolic pressure and systolic and diastolic diameters were increased after administration of phenylephrine in both thyroid states while fractional shortening declined, as would be expected in response to the increase in afterload. Because of the larger initial dimensions and higher aortic pressures in thyrotoxic animals, values for peak wall stress were markedly increased at both dosages of phenylephrine.

Effects of thyroxine on the venous system. Representative tracings obtained during determination of MCFP in the same calf before and after treatment with thyroxine are illustrated in Fig. 3. In the euthyroid state (Fig. 3, left), rapid injection of 150 mg acetylcholine into the pulmonary artery stopped the

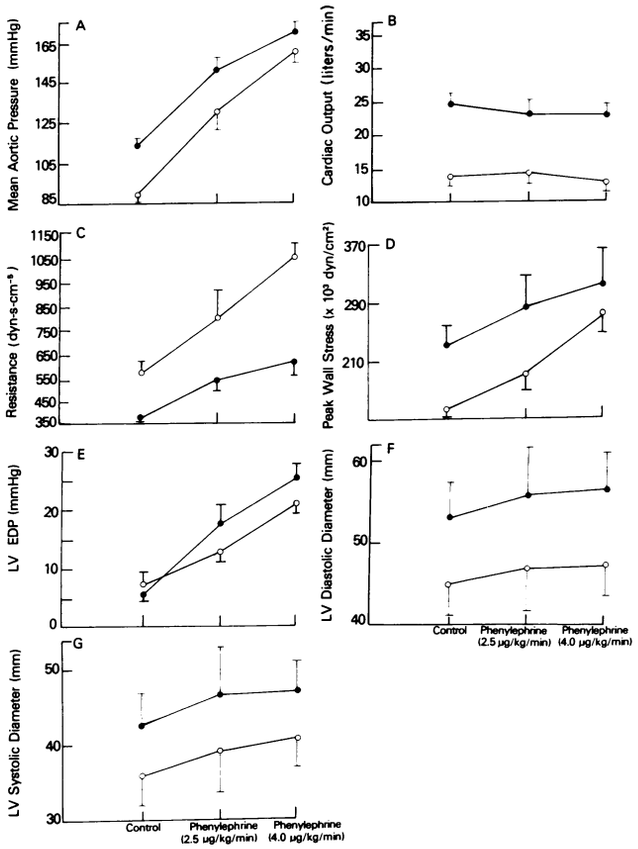

Figure 2. Effects of increasing systemic vascular resistance by infusion of graded doses of phenylephrine in six calves before (○) and after (●) 2 wk of treatment with thyroxine. (*A*) Mean aortic pressure, (*B*) cardiac output, (*C*) peripheral vascular resistance, (*D*) LV wall stress, (*E*) LV end-diastolic pressure, (*F*) LV diastolic diameter, and (*G*) LV systolic diameter. Means±SE are indicated.

heart for ~7–8 s. During this period of arrest, the arterial and venous pressures reached plateaus, and the arterial pressure remained ~20 mmHg above venous pressure. In these intact animals, blood could not be pumped from the arterial to the venous side of the circulation, as described by Guyton (8), to reach the equilibrium pressure or MCFP. Therefore, MCFP was calculated by use of the two pressure plateaus and the fact that the compliance of the venous side of the system is estimated to be 30 times greater than the arterial side (see Methods). However, the amount added to the venous plateau by this procedure did not exceed 1 mmHg in any experiment.

After thyroxine treatment, there was an increase in aortic pressures and heart rate (Fig. 3, right). During acetylcholine-induced cardiac arrest, aortic pressures were essentially the same as in the euthyroid state, but the venous pressure plateau was 5 mmHg higher than in the euthyroid state, resulting in an increase in MCFP and PGVR.

Shown in Table III are group mean values±SE for RA and aortic pressures after cardiac arrest in both thyroid states. Calculated values for MCFP and PGVR also are shown. The average values for aortic pressure did not change after thyroxine treatment, while the RA pressure, MCFP, and PGVR were increased significantly ($P < 0.01$). Values for MCFP and PGVR averaged ~6 and 4 mmHg, respectively, greater during thyrotoxicosis than in the euthyroid state.

To determine whether or not activation of sympathetic vasomotor reflexes played a role in the increase in MCFP, measurements of MCFP were repeated in three calves after ganglionic blockade with trimethaphan (2.0 mg/kg per min). In the euthyroid state after acetycholine-induced arrest, RA pressure was 8±2 mmHg, aortic pressure, 26±4 mmHg; MCFP, 8±2 mmHg; and PGVR, 9±1 mmHg. Comparable values in the thyrotoxic state were: RA pressure, 12±1 mmHg; aortic pressure, 21±1 mmHg; MCFP, 12±1 mmHg; and PGVR, 12±1 mmHg. Thus, there were comparable decreases in MCFP of ~25 and 20%, respectively, after acetylcholine-induced arrest in the euthyroid and thyrotoxic states.

Blood volumes changes. In six animals, blood volumes were measured by RISA before and after treatment with thyroxine (Table IV). Mean blood volume was 65±4 ml/kg in the euthyroid state and increased to 81±6 ml/kg after thyroid hormone ($P < 0.05$). On the average, plasma volume and erythrocyte mass also were greater in the thyrotoxic state.

Discussion

The results present the first systematic attempt to evaluate the role of changes in the arterial and venous compartments in maintaining the high output state associated with thyrotoxicosis. These results deserve further comment in terms of earlier studies of the peripheral circulation in thyrotoxicosis and the usefulness of venous return curves and cardiac function curves in understanding this unique high output state.

Theilen and Wilson (13) suggested that phenylephrine, a relatively pure alpha-adrenergic agonist, might be used to separate central vs. peripheral mechanisms in thyrotoxicosis. They reasoned that if the increase in cardiac output was secondary to peripheral vasodilation, then a purely vasoconstricting drug should cause a disproportionate decrease in the cardiac output of thyrotoxic patients. Conversely, if the higher output were caused primarily by a direct action of thyroid hormone on myocardial performance, vasoconstriction should not cause an appreciable change in cardiac output. They found that increases in mean arterial pressure of ~50 mmHg caused insignificant changes in the cardiac index of euthyroid subjects. However, a similar increase in arterial pressure in thyrotoxic patients produced an average decrease in cardiac index of ~34%. The resultant cardiac index was identical to the value obtained in euthyroid subjects. However, these workers failed to appreciate that "normalizing" vascular resistance in the two thyroid states would produce a disportionately greater increase in afterload in the thyrotoxic heart, which is illustrated by the present study.

Table II. Effects of Phenylephrine in Euthyroid and Thyrotoxic Calves

	Euthyroid			Thyrotoxic		
	Control	Phenylephrine (2.5 μg/kg/min)	Phenylephrine (4.0 μg/kg/min)	Control	Phenylephrine (2.5 μg/kg/min)	Phenylephrine (4.0 μg/kg/min)
Heart rate (*beats/min*)	95±5	91±9	91±9	146±6	146±6	146±6
LV systolic pressure (*mmHg*)	114±4	154±4*	201±4§	148±6	174±8	206±10*
LV end-diastolic pressure (*mmHg*)	6±1	13±1*	22±3*	7±2	18±4*	25±2*
Aortic pressure systolic (*mmHg*)	113±4	154±5‡	200±5‡	150±5	178±9	208±9‡
Aortic pressure diastolic (*mmHg*)	73±7	103±6*	140±5*	94±5	140±6*	146±9*
Aortic pressure mean (*mmHg*)	90±4	131±9‡	161±5‡	115±6	152±6†	171±5‡
Cardiac output	14.1±1.4	14.6±1.4	13.2±1.2	24.7±1.4	23.3±2.1	23.2±1.6*
Stroke volume (*ml*)	150±16	157±15	141±13	174±13	163±17	163±16
Systemic vascular resistance (dyn/cm^5)	563±65	814±92	1,046±118*	386±30	550±53*	602±34*
LV diastolic diameter (*mm*)	45±4	47±5*	47±4‡	53±4	56±6*	57±5*
LV systolic diameter (*mm*)	36±4	39±5*	41±4‡	43±4	47±6*	47±4‡
Fractional shortening	0.21±0.02	0.18±0.02	0.15±0.01	0.21±0.02	0.18±0.02	0.16±0.01
Peak wall stress ($\times 10^3$ dyn/cm^2)	143±12	193±24*	274±27*	232±27	284±44	315±50

Values represent mean±SE for six calves before and after treatment with thyroxine (200 μg/kg/d) for 12–14 d. *P* values were calculated on the basis of Dunnett's test for multiple comparisons with a control. *$P < 0.05$ Refers to comparison between phenylephrine infusion and control thyroid state. ‡$P < 0.01$. §$P < 0.001$.

Shown in Table II are the results of intravenous infusions of phenylephrine before and after 2 wk of thyroxine treatment. In the euthyroid state, an increment of 70 mmHg in mean arterial pressure produced no significant change in cardiac output. This is explained by the fact that LV dimensions and end-diastolic pressure were increased during the pressor infusion, which would tend to maintain forward blood flow by the Frank-Starling mechanism. Because of these compensatory adjustments, peripheral vascular resistance is not a major determinant of cardiac output within the the normal physiological operating range of the heart (14). On the other hand, as increases in afterload approach the ability of the myocardium to develop tension, cardiac output will decline. In thyrotoxic animals at the higher level of phenylephrine infusion (4.0 μg/kg/per min), cardiac output decreased by 6%, but peak wall stress was 120% greater than the euthyroid control value. Smaller, but qualitatively similar effects on LV function were observed in euthyroid animals. Thus, the high cardiac output in thyrotoxicosis is relatively independent of changes in peripheral resistance and the slight decrease obtained upon normalizing resistance is probably related to the marked increase in afterload produced by the pressor infusion.

Compared with the normal young animals used in this study, many of the patients studied by Theilen and Wilson (13) also may have had some reduction in myocardial functional capacity associated with aging, the duration of their illness, or the presence of other forms of heart disease. This may have contributed to the greater effect of pressor infusion on cardiac output observed in their study.

The part played by the systemic venous system in the high output state associated with thyrotoxicosis has received little attention. Frey (15) studied hand blood flow and venomotor tone in nine uncomplicated cases of thyrotoxicosis before and after therapy. Venomotor tone (Δpressure/Δvolume) was assessed during changes in hand volume produced by inflation of an occluding cuff and recorded with a hand plethysmograph. Despite a 50% reduction in hand blood volume after treatment, no significant changes were found in venomotor tone or in the initial peripheral venous pressure. This result was somewhat unexpected, since it had been hypothesized that constriction of capacitance vessels might be a factor in increasing venous return.

In the present study, we have evaluated the role of the venous system by measuring MCFP and PGVR. MCFP is the pressure measured in the circulatory system when the circulation has

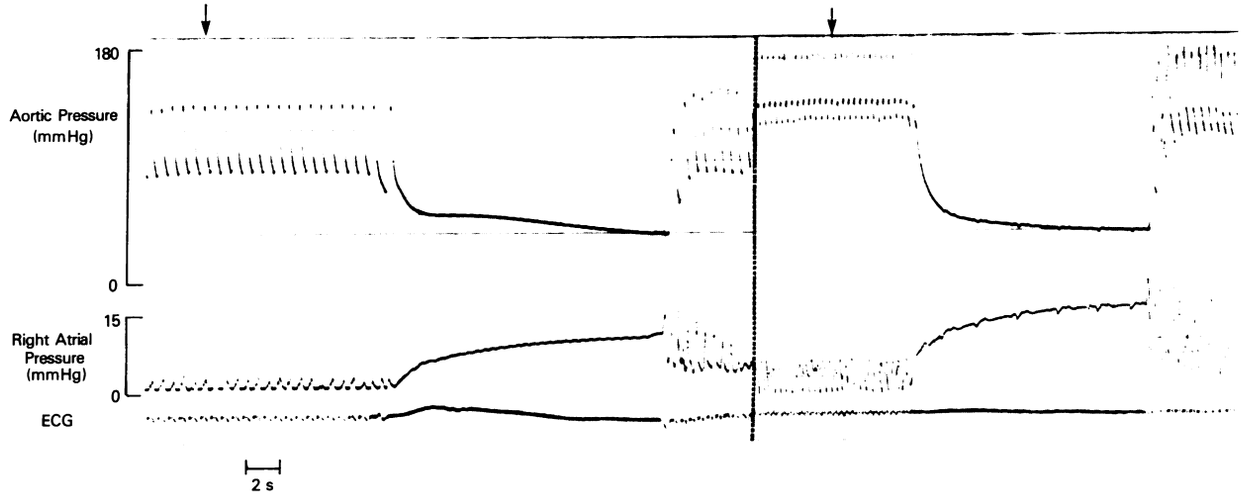

Figure 3. Representative records of MCFP determinations from a single calf before (*left*) and after (*right*) treatment with thyroxine for 2 wk. Shown are arterial pressure and right atrial pressure. Cardiac arrest was induced by rapid injection (arrow) of 150 mg acetylcholine into the pulmonary artery. In each case, the heart was stopped for ~7–8 s, during which the RA pressure rose to a plateau value. This value was ~5 mmHg higher after treatment with thyroxine. During the same period, arterial pressure fell to ~30 mmHg. Equilibrium values for the two pressures, which is the MCFP, was obtained using the formula given in Methods.

been arrested and pressures in all the compartments are in equilibrium. This measurement is a function of the unstressed volume, compliance, and the volume of blood in the system. The unstressed volume is the volume of blood in the system when MCFP equals zero and represents ~85% of the normal blood volume in anesthetized dogs (16, 17). The hemodynamic importance of MCFP is that it, minus RA pressures, determines the PGVR. Because under steady state conditions venous return must be equal to cardiac output, MCFP is a major determinant of cardiac output.

The average value for MCFP obtained here in lightly anesthetized euthyroid calves (10±1 mmHg) is similar to that obtained using acetylcholine arrest by Young et al. (10) in sedated dogs (9.9±1.6 mmHg). Since acetylcholine has a variety of actions on the circulation and nervous system that potentially could affect values for MCFP, these workers also measured MCFP in pentobarbital-anesthetized dogs in which the heart had been arrested by acetylcholine or by electrical fibrillation. No differences in values for MCFP were found between the two methods for producing arrest.

In the thyrotoxic state, an average increase of 6 mmHg in MCFP was observed (Table III). The relatively small increase in blood volume (20%) found in thyrotoxicosis, which is similar to that reported in thyrotoxic subjects (18), probably is not an adequate explanation for the large increase in MCFP. Chronic increases in blood volume of 20% in otherwise normal dogs have been reported to have little effect on MCFP (19). In the normal situation, stress-relaxation occurs in the veins, increasing their capacity sufficiently to accommodate the extra blood volume. In thyrotoxicosis, venous compliance apparently does not increase to the same extent, producing an increase in MCFP. This is not related primarily to an increase in autonomic ve-

Table III. Pressure Measurements in Euthyroid and Thyrotoxic Calves after Acetylcholine-induced Cardiac Arrest

	Euthyroid	Thyrotoxic	*P* Values
RA pressure (*mmHg*)	8±2	13±3	<0.01
Aortic pressure (*mmHg*)	28±2	26±2	NS
Mean circulatory filling pressure (*mmHg*)	10±1	16±2	<0.01
Pressure gradient for venous return (*mmHg*)	10±1	14±2	<0.02

Values are mean±SE for six calves before and after treatment with thyroxine (200 μg/kg) for 12–14 d.

Table IV. Body Weight, Blood Volume, Plasma Volume, and Erythrocyte Mass in Euthyroid and Thyrotoxic Calves

	Euthyroid	Thyrotoxic	*P* Value
Body weight (*kg*)	120.6±9.3	99.6±7.7	<0.001
Blood volume (*ml/kg*)	65±4	81±6	<0.05
Plasma volume (*ml/kg*)	47±4	65±3	<0.01
Erythrocyte mass (*ml/kg*)	18±1	21±1	<0.05

Values are mean±SE for six calves before and after treatment with thyroxine (200 μg/kg) for 12–14 d.

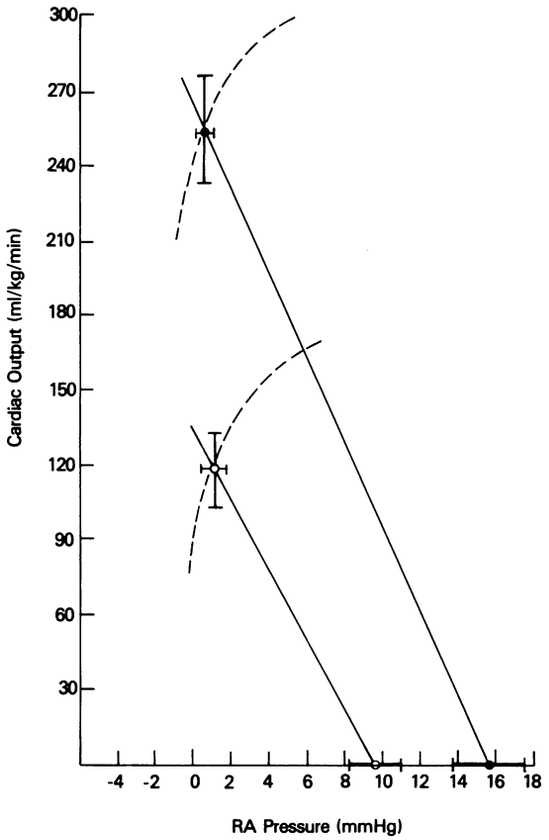

Figure 4. Cardiac function and venous return curves for the euthyroid and thyrotoxic states. Hypothetical cardiac function curves were constructed to fit through measured values from Tables I and III for RA pressure and cardiac output in the euthyroid (○) and thyrotoxic (●) states before and after acetylcholine-induced cardiac arrest. The average value for the normal cardiac output is represented by the intersection of the cardiac function and venous return curves. The increased cardiac output observed in thyrotoxic animals is the result of a combination of increased myocardial contractility and alterations in the characteristics of the peripheral venous compartment. This is represented by the intersection of the venous return curve in the thyrotoxic state with a new cardiac function curve which is displaced upward and to the left.

nomotor tone since MCFP decreased only ~25% after ganglionic blockade in thyrotoxicosis, which was similar to the 20% decrease observed in euthyroid animals.

To integrate the observed changes in the venous circulation and heart, the graphic approach originally described by Guyton (8) would seem useful. Application of this analysis by construction of venous return and cardiac function curves is shown in Fig. 4. Average values for euthyroid and thyrotoxic animals from Table III have been used to construct these graphs. The venous pressure at zero blood flow or MCFP was measured when the circulation was stopped by injection of acetylcholine. By recording RA pressure and cardiac output just prior to acetylcholine injection, the second point needed to construct the venous return curve was obtained.

Hypothetical cardiac function curves, which are given for illustrative purposes in Fig. 4, were drawn so as to pass through measured values of RA pressure and cardiac output. The point at which the venous return curve intersects the cardiac function curve defines the cardiac output that would be produced by that set of curves. In the euthyroid state, the venous return curve intersects the cardiac function curve to produce a normal cardiac output for the calf of ~14 liters/min at an RA pressure of ~1 mmHg. After treatment with thyroxine for 2 wk, the MCFP was increased, shifting the venous return curve to the right along the pressure axis. RA pressure before arrest was changed very little so in thyrotoxicosis the slope of the venous return curve, which is inversely related to venous resistance, is essentially normal. The increase in MCFP observed after thyroxine treatment is similar to that described in other high output states, such as arteriovenous fistula (20) and anemia (21). However, in the latter conditions, the slope of the venous return curve is markedly increased because of the decrease in venous resistance.

In principle, displacement of the venous return curve to the right should cause some increase in cardiac output because the venous curve would intersect the cardiac function curve at a higher level. This effect is illustrated as the point at which the venous return curve in thyrotoxicosis intersects the normal cardiac function curve in Fig. 4. The theoretical increase in cardiac output in this circumstance would be ~40%. However, the positive inotropic action of thyroid hormone (3) causes the cardiac function curve to be displaced upward and to the left. The new venous return curve then intersects the new cardiac function curve at a twofold higher value for cardiac output. Thus, the characteristic high cardiac output associated with thyrotoxicosis is produced by a different combination of actions on the systemic venous circulation and heart than those found in other high output states.

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