Cardiovascular response to exogenous serotonin in healthy calves

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Objective—To characterize the cardiovascular response to IV administration of serotonin (5-hydroxytryptamine [5-HT]) in calves.

Animals—5 healthy unsedated Friesian calves.

Procedure—41 5-HT administrations were performed: 11 slow infusions (duration, 5 minutes) and 30 bolus infusions (duration, 5 seconds). Cardiovascular function values were recorded before, during, and after the infusions.

Results—Slow infusion of 5-HT first resulted in a brief period of severe bradycardia, then in sustained tachycardia with a concomitant increase in cardiac output. Systemic blood pressure response to 5-HT was triphasic, with initial hypotension concomitant with bradycardia, then a pressor phase associated with an increase in systemic vascular resistance, and finally, a long-lasting hypotensive phase associated with decreased systemic vascular resistance. Pulmonary hypertension was associated with increased pulmonary vascular resistance, reflecting intense pulmonary vasoconstriction. Bolus infusion at increasing dosages resulted in dose-dependent bradycardia and systemic hypotension, followed by dose-dependent systemic hypertension. Unlike with slow infusion, neither the second tachycardic nor the third systemic hypotensive phases were evident.

Conclusions—5-HT induces dose-dependent cardiovascular responses, including a reflex response followed by pulmonary and systemic vasoconstriction, in healthy calves.

Clinical Relevance—Determining the type of serotonergic receptors responsible for these responses may help to determine whether 5-HT is involved in the mechanisms underlying brisket disease in cattle. (*Am J Vet Res* 1996; 57:731–738)

Serotonin (5-hydroxytryptamine [5-HT]) is a vasoactive amine originally isolated from clotted blood.[1] This monoamine is known to exert complex and multiple actions on cardiovascular function.

The major peripheral action of 5-HT appears to be on the blood vessel wall. A 5-HT-induced vasoconstriction may be mediated by direct activation of serotonergic[2] or adrenergic[3] receptors, by amplification of the vasoconstrictor responses of other neurohumoral mediators,[4] or by an indirect sympathomimetic effect.[5] Vasodepressor responses to 5-HT also have been reported in various species.[6] The major mechanisms by which 5-HT elicits vasodilatation are through actions at vascular smooth muscle, endothelial cells, and sympathetic adrenergic nerve terminals.[6]

The effect of 5-HT on arterial blood pressure usually is triphasic, consisting of an initial transient hypotension, a pressor phase, and a final sustained depressor phase.[7] Because 5-HT may act on the heart, blood vessels, or central vasomotor function[8] and evokes potent reflexes,[9] the blood pressure response will differ, according to species and experimental circumstances.[10-12]

The effect of 5-HT on heart rate (HR) consists of brady- or tachycardia. In most species, the main initial response to 5-HT is brief bradycardia, associated with systemic hypotension.[13-15] After this bradycardic episode, 5-HT induces tachycardia in most animals studied.[11,16-19] In calves, bradycardic,[20] as well as tachycardic,[21] responses to 5-HT have been described.

Information regarding serotonergic mechanisms in hemodynamics in cattle has been rare and confusing. This is surprising in view of its possible involvement in hypoxic pulmonary vasoconstriction, which is a key physiopathological mechanism in pulmonary diseases such as brisket disease.[22] In this context, the knowledge of serotonergic mechanisms constitutes a basic requirement for a better understanding of the physiopathologic processes in the development and treatment of respiratory diseases in cattle.

The purpose of the study reported here was to characterize the cardiovascular effects of 5-HT infusion in healthy calves. This would be the necessary prerequisite step for determining which serotonergic receptors are involved in these effects (by use of specific antagonists) and, in a second step, for testing receptor antagonists in field studies.

Materials and Methods

Calves—Five Friesian calves that weighed 315.6 ± 12.3 kg (mean ± SD) and that were considered healthy, as determined by clinical history and lack of abnormalities on physical examination, auscultation, and electrocardiography, were studied. At 1 month of age, all calves were anesthetized with xylazine-guaifenesin-thiopental, and the right common carotid artery was exteriorized in the midcervical region and maintained in a subcutaneous location by closure of the underlying muscles.

Twenty-four hours before the study, an arterial catheter[a] and 2 introducers[b] were inserted percutaneously into the previously transposed artery and into the left jugular vein, respectively, using the Seldinger technique,[23] under local analgesia. Another catheter[c] was inserted into the right jug-

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ular vein for drug infusions. Food was withheld for 12 hours before the study began to diminish eructation and rumination that hampers reliability of esophageal pressure measurements. All calves were studied while standing in a stanchion. Neither anesthesia nor sedation was used, and the calves remained catheterized between protocols.

Instrumentation—The ECG[d] was obtained by use of a bipolar base-apex lead. Mean, systolic, and diastolic systemic arterial blood pressure (SAP_M, SAP_S, and SAP_D, respectively) were obtained from an extravascular pressure transducer[e] and amplifier-monitor system.[f] The SAP and ECG were displayed on the screen of a rapid-writing polygraph,[g] allowing continuous monitoring of these measurements during right ventricle catheterization procedures. Mean pressures were calculated from at least 20 consecutive cardiac cycles.

A balloon-tipped, triple-lumen Swan-Ganz catheter[h] was inserted in the left jugular vein through the first introducer. The position of the catheter was ascertained by identification of the characteristic pressures[24] measured via an extravascular pressure transducer[i] and amplifier-monitor system[j] connected to the polygraph. The distal tip of the catheter was advanced into the right ventricle. After inflation of the balloon, the tip of the catheter was directed into the pulmonary artery, 4 to 5 cm distal from the pulmonary valve. The balloon then was deflated for measurement of the pulmonary artery pressure (PAP) and blood temperature. Pulmonary capillary wedge pressure (PW) was obtained by inflating the balloon and advancing the catheter until a characteristic wedge tracing[24] was evident on the polygraph, and was recorded during 2 to 3 respiratory cycles.

A flush catheter[k] was passed into the left jugular vein through the second introducer. On the basis of the characteristic pressure wave recorded via an extravascular pressure transducer[l] connected to the polygraph, the tip of this catheter was advanced into the right ventricle, then back into the right atrium. This catheter was used to measure central venous pressure (CVP) and to inject iced 5% glucose solution for cardiac output (CO) determinations. The CO was measured by a CO thermodilution computer,[m] according to the procedure previously described by Amory et al.[25] Briefly, iced 5% glucose solution[n] (dosage, 5 ml/100 kg of body weight) was administered by bolus injection into the right atrium, via the flush catheter, by means of a compressed-air-driven pump triggered by the R wave of the ECG. The thermodilution curve was measured by means of the thermistor mounted at the tip of the Swan-Ganz catheter. Five to 10 successive CO measurements were performed and mean was calculated. The continuous display of pulmonary artery blood temperature allowed monitoring of each thermodilution decay curve. The CO measurement was discarded when the thermodilution curve quality was poor.[26]

Prior to the catheterization procedure, each pressure transducer was calibrated against a water column and tested for linearity. The zero pressure was carefully standardized at the level of the calf's scapulohumeral joint.

Calculations—Heart rate was calculated from the ECG tracings. The PW and CVP were calculated by planimetry from their respective tracings. Stroke volume (SV) and cardiac index (CI) were determined from the ratio of CO to HR and to body weight, respectively. Pulmonary and systemic vascular resistance (PVR and SVR, respectively, in dyne·s·cm^{-5}) were calculated by use of standard formulas[24]:

$$PVR = \frac{PAP - PW}{CO} \times 10 \times 1.332,$$

$$SVR = \frac{SAP - CVP}{CO} \times 60 \times 1.332,$$

where pressures were in millimeters of Hg, and CO in liters per minute.

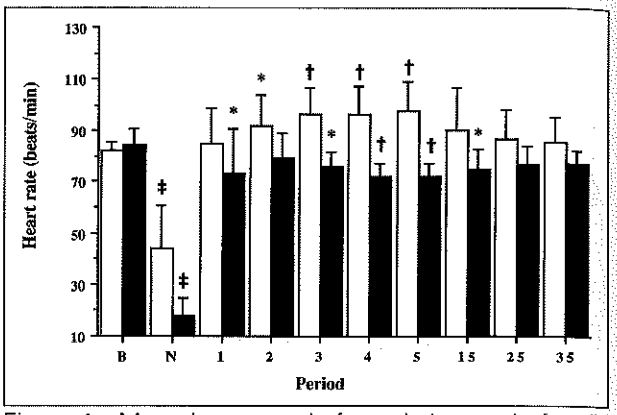

Figure 1—Mean heart rate before, during, and after IV administration of serotonin (5-hydroxytryptamine [5-HT]) in calves. □ = slow infusion (duration, 5 minutes); ■ = bolus infusion (duration, 5 seconds). Bars indicate SD. B = baseline; N = nadir. Numerals indicate elapsed time (in minutes) after start of 5-HT infusion. *, †, ‡Significantly ($P \leq 0.05$, 0.01, 0.001, respectively) different from baseline value.

Table 1—Mean (± SD) cardiovascular responses to slow IV infusion of serotonin (5-hydroxytryptamine [5-HT] in healthy calves

Variable		Baseline	Elapsed time from start of infusion (min) 3 to 5	15
CO	(L/min)	42.9 ± 2.7	49.4 ± 7.7*	42.0 ± 4.8
CI	(ml/min·kg)	131.4 ± 10.5	151.3 ± 24.8*	128.7 ± 14.4
SV	(ml/beat)	523 ± 30	516 ± 90	471 ± 53
CVP	(mm of Hg)	−0.60 ± 3.63	5.55 ± 5.93*	−2.03 ± 2.63
PW	(mm of Hg)	10.9 ± 1.0	13.8 ± 4.9	11.4 ± 1.4

*Significantly different from baseline value at $P \leq 0.001$.
CO = cardiac output; CI = cardiac index; SV = stroke volume; CVP = central venous pressure; and PW = pulmonary capillary wedge pressure.

After cardiovascular instrumentation, the calf stood undisturbed for 15 minutes before baseline measurements were obtained. Baseline pressures and CO were recorded only when HR was within the resting range.[27]

Experimental design—Intravenous infusions of 5-HT-creatinine sulfate complex[o] were performed through the right jugular catheter by means of a perfusion pump.[p] Dosages were expressed as active base of 5-HT.

In all calves, a protocol that consisted of IV infusion of 5-HT (50 µg/kg·min over 5 minutes) was used first. A total of 11 infusions was performed for all calves. The second protocol consisted of a series of 6 successive IV bolus infusions of 5-HT per calf (50, 50, 50, 12.5, 25, and 50 µg/kg, each over 5 seconds). Bolus infusions were performed at 45-minute intervals to allow hemodynamic values to return to baseline.

Data were recorded continuously from the beginning of 5-HT administration to 35 minutes after. All the cardiovascular values described previously were recorded for the first protocol, and HR and $SAP_{M,S,D}$ for the second protocol.

Statistical analysis—Data were reported as mean ± SD. The effect of 5-HT on hemodynamics as well as the possibility of tachyphylaxis were tested by use of ANOVA for repeated measures.[28] When significant F values were obtained, means were compared, using Fisher test. Significance was defined as $P \leq 0.05$.

To test the effect of increasing the dosage of 5-HT on hemodynamic values, a random linear model, with dosage as a covariable, was fitted to the data[29] and analyzed using a computer program.[30] Data from the 3 last bolus injections

Table 2—Mean (± SD) systemic arterial pressure (SAP; in mm of Hg) response to 5-HT administered as a slow or a bolus infusion in healthy calves

SAP	Baseline	Nadir	Elapsed time from start of infusion (min) 1	2	3	4	5	15	25	35
Mean										
Slow	117.9 ± 3.7	91.5 ± 15.4*	160.2 ± 32.7*	153.0 ± 25.9*	146.2 ± 24.9*	143.6 ± 23.3*	140.2 ± 21.7†	100.1 ± 7.0‡	105.4 ± 3.6	111.7 ± 3.6
Bolus	122.0 ± 2.5	79.8 ± 22.4*	186.7 ± 15.5*	149.6 ± 20.8†	131.8 ± 18.0	125.1 ± 12.3	122.8 ± 11.3	121.5 ± 6.8	119.9 ± 7.2	122.0 ± 5.8
Systolic										
Slow	154.5 ± 3.7	153.7 ± 7.6	209.6 ± 33.5*	209.5 ± 18.4*	211.7 ± 17.9*	214.6 ± 19.2*	212.0 ± 25.1*	147.9 ± 21.0	151.7 ± 13.6	152.5 ± 10.6
Bolus	164.9 ± 4.9	174.4 ± 32.8	243.9 ± 30.8*	202.6 ± 23.6*	183.6 ± 24.4‡	178.8 ± 20.3	171.8 ± 20.3	161.0 ± 15.2	160.1 ± 14.1	164.4 ± 10.7
Diastolic										
Slow	95.4 ± 4.9	55.0 ± 17.0*	122.0 ± 35.8*	116.1 ± 28.9†	105.6 ± 26.2	102.5 ± 26.8	99.7 ± 24.0	72.9 ± 9.9†	82.3 ± 6.6	89.1 ± 7.2
Bolus	98.4 ± 0.8	50.8 ± 13.3*	146.5 ± 17.6*	114.0 ± 17.1	100.8 ± 19.0	92.8 ± 16.3	90.8 ± 11.2	95.6 ± 8.3	92.5 ± 8.2	96.8 ± 7.6

*,†,‡Significantly different from baseline value at $P \leq 0.001$, $P \leq 0.01$, and $P \leq 0.05$, respectively.
Data are from the first bolus infusion only.

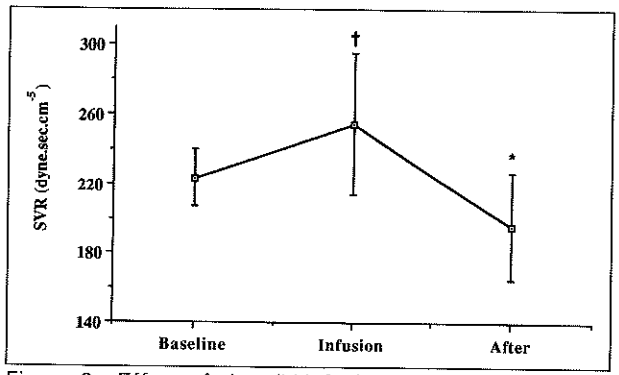

Figure 2—Effect of slow IV infusion of 5-HT on systemic vascular resistance (SVR) in healthy calves. Mean values were calculated before the infusion (baseline), between the third and the fifth minute of infusion (infusion), and 15 minutes after the infusion (after). *See* Figure 1 for key.

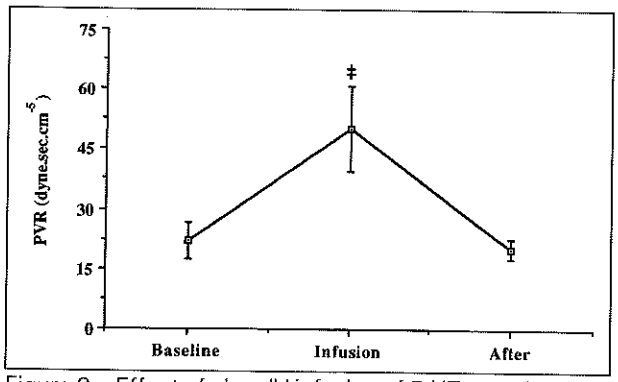

Figure 3—Effect of slow IV infusion of 5-HT on pulmonary vascular resistance (PVR) in healthy calves. *See* Figure 1 for key.

(12.5, 25, and 50 μg/kg) were used. The linear model was, in general form:

$$Y_{ij} = m + a_i + b\,(X_{ij} - X) + e_{ij},$$

where Y = hemodynamic value, m = overall mean, a_i = random effect of the i^{th} individual, b = linear regression coefficient for hemodynamic value on dosage (X), and e_{ij} = residual error. One-way ANOVA (including the effect of the day of measurement) also was applied to the data, to compare data from infusions performed on different days.

Results

Clinical effects—During bolus and slow infusion of 5-HT, apnea was observed 10 to 25 seconds after the start of the infusion. However, 5-HT-induced apnea was more prolonged with bolus (14 ± 6 seconds) than with slow infusion (7 ± 2 seconds). With both types of infusion, apnea was followed by severe tachypnea beginning 19 ± 6 seconds (slow infusion) and 38 ± 7 s (bolus) after start of the infusion. Both types of infusion induced staggering, congestion of conjunctivae, and lacrimation. Coughing was observed in 3 of 5 calves during the first minute after bolus infusion and in 1 of 5 calves during the first minute after the start of slow infusion of 5-HT. All calves passed liquid feces during or immediately after the end of the slow infusion. Hemodynamic values at baseline were not significantly different among the different protocols.

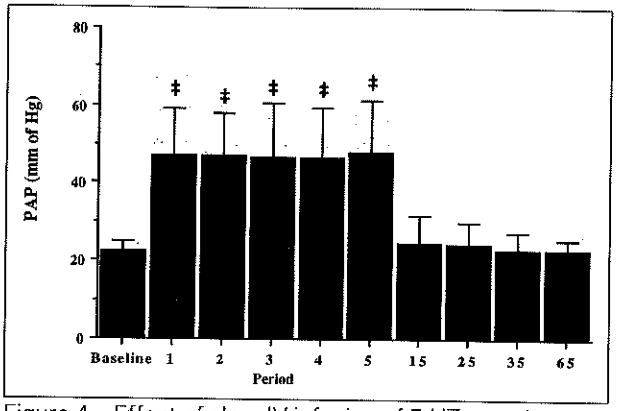

Figure 4—Effect of slow IV infusion of 5-HT on pulmonary artery pressure (PAP) in healthy calves. *See* Figure 1 for key.

Slow infusion—Functional response to 5-HT infusion was not significantly attenuated when infusions were repeated in the same calf at 1-day intervals. A brief period of severe bradycardia, concomitant with apnea, was observed 10 to 25 seconds after start of 5-HT infusion. Afterward, significant tachycardia was observed between 2 and 5 minutes into the infusion (Fig 1), with increased CO (Table 1). Simultaneous with the bradycardia, systemic hypotension was detected, followed by hypertension from the first to the fifth minutes of the 5-HT infusion (Table 2). The maximal hypertensive response (173.8 ± 26.6% of the baseline value) was always recorded by the first minute after the start of the infusion. A significant increase in SVR accompanied the hypertensive response (Fig 2).

The PVR and PAP were significantly increased during 5-HT exposure (Fig 3 and 4), although PW remained unchanged. Infusion of 5-HT also induced a significant increase in CVP. Except for a later phase of systemic hypotension associated with decreased SVR, all hemodynamic values had returned to baseline by 10 minutes after the end of the 5-HT infusion.

Table 3—Mean (± SD) cardiovascular responses of healthy calves to repeated administration of 5-HT, at a dosage of 50 µg/kg of body weight

Variable	Period*	Dose 1	2	3	4	P†
Heart rate (beats/min)	Baseline	84.5 ± 6.3[a]	85.1 ± 6.9[a]	81.6 ± 8.6[a]	79.0 ± 8.6[a]	NS
	1	73.4 ± 17.5[a]	72.8 ± 14.0[a]	72.6 ± 17.1[a]	68.4 ± 17.9[a]	NS
	2	79.4 ± 9.8[a]	80.4 ± 8.0[a]	79.5 ± 11.4[a]	73.3 ± 11.7[a]	NS
	3	75.9 ± 5.5[a]	75.4 ± 5.6[a]	74.8 ± 9.7[a]	69.9 ± 8.5[a]	NS
	4	72.0 ± 5.0[a]	72.0 ± 6.7[a]	72.5 ± 9.4[a]	67.6 ± 9.3[a]	NS
	5	72.2 ± 4.9[a]	72.9 ± 7.7[a]	72.3 ± 9.7[a]	67.0 ± 9.7[a]	NS
	15	75.1 ± 7.7[a]	79.0 ± 13.3[a]	74.2 ± 9.8[a]	69.5 ± 9.5[a]	NS
	25	76.6 ± 7.3[a]	82.1 ± 12.2[a]	82.1 ± 10.5[a]	76.3 ± 14.1[a]	NS
Mean SAP (mm of Hg)	Baseline	122.0 ± 2.5[a]	123.4 ± 4.1[a]	124.4 ± 3.0[a]	121.7 ± 9.2[a]	NS
	1	175.6 ± 10.7[a]	166.9 ± 6.7[b]	166.0 ± 13.1[b]	161.5 ± 12.4[b]	≤ 0.05
	2	151.7 ± 19.1[a]	139.7 ± 17.4[b]	139.1 ± 16.1[b]	139.2 ± 13.5[b]	≤ 0.01
	3	131.8 ± 18.0[a]	125.0 ± 12.4[b]	125.1 ± 11.3[b]	121.8 ± 13.2[b]	≤ 0.05
	4	125.1 ± 12.3[a]	118.4 ± 10.5[a]	118.6 ± 9.1[a]	116.8 ± 11.4[a]	NS
	5	124.4 ± 11.2[a]	118.1 ± 12.8[a]	117.7 ± 12.2[a]	115.7 ± 10.7[a]	NS
	15	119.9 ± 7.2[a]	117.5 ± 3.1[a]	118.1 ± 4.8[a]	115.3 ± 8.8[a]	NS
	25	122.0 ± 5.8[a]	120.6 ± 5.1[a]	120.8 ± 4.1[a]	117.7 ± 8.8[a]	NS

*Numerals indicate elapsed time (in minutes) after 5-HT bolus administration. †For effect of repeated administration.
NS = not significant.
For each period, values with different superscripts are significantly ($P \leq 0.05$) different.

Table 4—Mean (± SD) cardiovascular responses of healthy calves to administration of 5-HT at increasing dosages

Variable	Period*	Dosage (µg/kg) 12.5	25	50	r^2	P†
Heart rate (beats/min)	Baseline	82.6 ± 10.0	80.1 ± 5.3	79.0 ± 8.6	0.03	NS
	Nadir	25.5 ± 4.5‡	19.3 ± 7.5‡	15.3 ± 4.2‡	0.37	≤ 0.01
	1	74.8 ± 8.9§	67.6 ± 16.5‖	68.4 ± 17.9§	0.03	NS
	2	75.8 ± 18.3	70.4 ± 8.3§	73.3 ± 11.7	0.00	NS
	3	72.6 ± 8.9§	68.3 ± 8.2‖	69.9 ± 8.5§	0.01	NS
	4	74.5 ± 9.7§	67.4 ± 6.2‖	67.6 ± 9.3‖	0.09	NS
	5	70.9 ± 9.1‖	65.9 ± 5.3‡	67.0 ± 9.7‖	0.03	NS
	15	75.8 ± 8.0	72.6 ± 11.4	69.5 ± 9.5§	0.08	NS
	25	76.0 ± 12.1	71.7 ± 10.8§	76.3 ± 14.1	0.00	NS
Mean SAP (mm of Hg)	Baseline	124.6 ± 4.6	121.3 ± 7.0	121.7 ± 9.2	0.02	NS
	Nadir	95.4 ± 11.9‡	83.8 ± 28.6‡	75.2 ± 27.9‡	0.12	≤ 0.05
	Peak	137.8 ± 11.9‖	162.0 ± 11.6‡	180.4 ± 14.4‡	0.66	≤ 0.001
	1	127.8 ± 8.3	148.6 ± 12.0‡	161.5 ± 12.4‡	0.60	≤ 0.01
	2	122.9 ± 6.8	129.2 ± 14.3	139.2 ± 13.5§	0.28	≤ 0.05
	3	122.0 ± 4.8	121.4 ± 10.6	121.8 ± 13.2	0.00	NS
	4	121.5 ± 8.3	119.3 ± 8.4	116.8 ± 11.4	0.00	NS
	5	123.0 ± 7.5	121.5 ± 12.7	115.7 ± 10.7	0.10	NS
	15	117.5 ± 4.9	123.4 ± 9.7	115.3 ± 8.8	0.03	NS
	25	121.0 ± 7.0	119.6 ± 8.1	117.7 ± 8.8	0.03	NS

†For effect of dosage within period. ‡,§,‖Significant ($P \leq 0.001$, 0.05, and 0.01, respectively) difference between values at different periods within a dosage.
See Table 3 for key.

Bolus infusion—Within a minute of bolus infusion (at a dosage of 50 µg/kg), a brief period of severe bradycardia was observed, concurrent with apnea. Afterward, significant bradycardia was observed between 1 and 15 minutes after bolus infusion (Fig 1). Simultaneously, systemic hypotension was detected, which was followed by hypertension within the first 2 minutes after bolus infusion (Table 2). The maximal hypertensive response was found a few seconds after the hypotensive phase, before the first minute after infusion.

The HR responses to repeated doses of 5-HT remained similar. On the other hand, the SAP_M responses to repeated administration of 5-HT were significantly reduced, comparing the response induced by the first bolus with that induced by the 3 following boluses (Table 3).

Administration of 5-HT at increasing dosages resulted in dose-dependent decrease in the nadir value of HR. Later, changes in HR did not seem to be dose-dependent. For SAP_M, the 5-HT-induced changes were dose-dependent during the first 2 minutes after injection (Table 4).

Discussion

Baseline systemic and pulmonary hemodynamic values measured in this study did not differ from reference values for calves of the same breed and body weight.[27] Baseline values for HR (79 to 85 beats/min), however, were less than those described from other studies (90 to 119 beats/min).[31,32] The CI values obtained in the present study were similar to those reported in several previous studies,[27,33] but higher than values reported in other studies.[34] Such differences may be attributable to the different methods used for CO determination,[35] but also to the age of the cattle, which must be considered to interpret CI absolute values.[27]

Because the cardiovascular response to slow infusion of 5-HT was not attenuated when infusions were repeated at 1-day intervals, we suggest that previous infusions did not influence the results of bolus

infusions performed 2 to 3 days later. However, the responses of SAP to repeated bolus administration of 5-HT were significantly different, when comparing the response induced by the first treatment with the responses induced by the 3 subsequent treatments. A 5-HT-induced tachyphylaxis has been described by some investigators,[36] but not by others.[37] In the latter study, sufficient time was allowed between successive 5-HT injections for hemodynamic values to return to baseline. However, our study clearly revealed evidence of blunted SAP responses to 5-HT, even with a 45-minute interval (with return to baseline values) between each administration.

A brief period of severe bradycardia, associated with hypotension and apnea, was observed 10 to 25 seconds after the start of slow 5-HT infusion. This triad of events represents the initial response elicited by IV 5-HT administration in many species with an intact autonomic nervous system.[13-15] In anesthetized cattle[38] and in the conscious cattle in our study, 5-HT induced comparable severe bradycardia and hypotension. Several studies[10,39] have revealed that these effects were abolished by vagotomy, ganglionic blockade, or muscarinic antagonists. This 5-HT-induced bradycardia was suggested to be attributable to a Bezold-Jarisch-like reflex originating from depolarization of cardiac vagal afferents.[40,41] Subsequent studies[17,42,q] have provided evidence for the involvement of 5-HT_3 receptors in the initiation of this reflex. However, the triad of events also could result from activation of pulmonary chemoreflexes,[43] because 5-HT has been described as effective in evoking this reflex in cats and rabbits.[44-46] Central application of 5-HT also has been shown to induce bradycardia and hypotension in rats,[47] probably through activation of central 5-HT_{1A} receptors.[48]

Immediately after the bradycardic response, 5-HT induced sustained tachycardia during the 5-minute slow infusion in all calves. The mechanisms by which 5-HT exerts its chronotropic effect on the heart are notoriously species-dependent.[15,17,18,49] Although unequivocally determining the mechanisms involved is not possible, our results suggested that 5-HT has a positive chronotropic effect in cattle, because the hypertension simultaneously recorded should have led to reflexic bradycardia. This 5-HT-induced tachycardic response in cattle was in striking contrast to the results of Greenlees et al,[20] who reported bradycardia during 5-HT infusion in cattle. In that study, however, 5-HT was administered directly in the pulmonary artery. This difference suggests that the concentration of 5-HT, which is metabolized by the pulmonary endothelial vascular bed,[50] may have been too low in the cardiac circulation to induce tachycardia.

In contrast to the tachycardic response to slow 5-HT infusion, HR decreased in response to 5-HT bolus infusions. The total bolus dose was 20% of that used in the slow infusion, precluding reliable comparison between most effects of administration procedures. However, comparison of the values recorded at 1 minute after the start of the infusion seems appropriate, because the total dose administered at that time was equal. Hence, we could predict that responses would be greater in magnitude, but briefer for the bolus injection. This was true for the hypertensive response to 5-HT recorded at 1 minute, but not for HR. Lack of tachycardia 1 minute after the bolus infusion could have resulted from a powerful bradycardic response that overshadowed 5-HT-induced tachycardic effects, as described in cats.[17] Conversely, tachycardia probably predominated after 1 minute of slow 5-HT infusion, because of a weaker bradycardic response.

Why the bradycardia persisted for > 15 minutes after 5-HT bolus administration, whereas the hypertensive response was maintained only for 2 minutes, is not known. The difference between the time course of these effects supported the view that the effect of 5-HT on HR and SAP could be mediated by different mechanisms.

During slow 5-HT infusion, SV was not significantly altered. Consequently, the increase in CO observed during slow 5-HT infusion could be explained only by the chronotropic response to 5-HT. Factors that determine SV in an intact healthy heart include preload, afterload, and myocardial contractility.[24] During 5-HT infusion, afterload was increased, as suggested by the increase in PVR, SVR, PAP, and SAP. As a result, SV would have tended to decrease. However, right ventricular preload also was increased, as suggested by the increase in CVP, which would have caused an increase in SV. Myocardial contractility was not evaluated in this study, although a positive inotropic effect of 5-HT has been described in previous studies.[51] The lack of change in SV probably resulted from a balance between these opposite effects.

Slow 5-HT infusion elicited a triphasic response, including a brief hypotensive phase, a pressor phase, and a depressor phase that was maintained after end of 5-HT infusion. With bolus infusion, the last hypotensive phase was not observed.

The initial hypotensive phase was observed with slow and bolus infusion both, but was more marked after bolus than after slow infusion. Bolus infusion with increasing dosages of 5-HT caused dose-dependent degrees of hypotension. A similar hypotensive response to 5-HT was described in anesthetized calves,[38] as in other species.[10,52] This initial hypotension was probably attributable to the abrupt bradycardia that was previously described, and to the related decrease in CO.

A hypertensive phase was detected immediately after the hypotensive one, and was sustained for the 5 minutes of the slow infusion. A dose-dependent hypertensive response also was observed with bolus administration. Amplitude of SAP change was greater 1 minute after the bolus than 1 minute after start of infusion. The 5-HT-induced hypertensive response could probably have resulted from the increased CO and SVR, the latter reflecting systemic vasoconstriction. Direct marked vasoconstrictor activity of 5-HT was demonstrated in isolated vascular preparations from various species,[53,54] including calves.[55] This vasoconstriction appears to be mainly attributable to direct activation of serotonergic receptors on smooth muscle cells.[2] This direct sensitivity to 5-HT varies among vascular tissues from different species and, within the same species, among blood vessels of different anatomic origin.[56,57] A study with specific antagonists revealed that contraction of isolated blood vessels in response to 5-HT, as well as the secondary pressor phase in intact animal, were related to activation of 5-HT_2 receptors.[58] However, vasoconstriction was demonstrated to be 5-HT_1-mediated in certain vessels, such as canine saphenous vein and

rabbit basilar arteries.[54,59] The contractile effect of 5-HT can be enhanced by hypoxia or moderate cooling.[60,61]

In addition to its direct contractile effects on vascular smooth muscle, 5-HT potentiates the contractile response to other vasoactive substances such as norepinephrine, histamine, angiotensin II, thromboxane A_2, and prostaglandin $F_{2\alpha}$.[4,62] This amplifying mechanism is inhibited by ketanserin, indicating that activation of 5-HT_2 receptors is required for its expression.[4] Serotonin also has been shown to induce vasoconstriction by direct and indirect activation of α-adrenergic receptors[5,63] or through the release of endothelium-derived constricting factors.[64] Free 5-HT also may enhance its own accumulation by aggregating platelets,[65] although aggregation of platelets does not necessarily imply secretion of mediators.

Although the predominant effect of 5-HT is to cause vasoconstriction, vasodilator properties of 5-HT also have been demonstrated in vitro and in vivo.[6] In our study, the pressor response to 5-HT was followed by a longer depressor phase, which was maintained after end of 5-HT infusion. Because at that time CO had returned to baseline values, this systemic hypotension could probably have resulted from the simultaneous decrease in SVR, reflecting systemic vasodilatation, which may have been elicited via direct or indirect mechanisms. Direct vasodilatation is mediated through serotonergic receptors on vascular smooth muscle.[66,67] The most potent dilator responses to 5-HT, however, are indirect, and involve endothelial cells that trigger the release of nitric oxide.[68] In addition, 5-HT is known to presynaptically inhibit the release of norepinephrine in response to nerve stimulation,[5,69] to induce the release of inhibitory transmitters from peptidergic nerves (eg, vasoactive intestinal peptide), and to stimulate production of prostacyclin.[57] The receptors that are responsible for this vasodilator response appear to be of the "5-HT_1-like" type. Accordingly, the ultimate hemodynamic response to 5-HT will be defined by the balance between these different effects.

Bolus infusion of 5-HT did not induce a third hypotensive phase, as observed after 5 minutes of slow 5-HT infusion. This suggests that in cattle, the late depressor effect of 5-HT could be elicited by doses much higher than those needed for the initial depressor and pressor effects.

The CVP was significantly increased during slow 5-HT infusion. This variable is influenced by the heart's ability to pump the blood returned to it, by venous return, and by peripheral vascular tone.[24] The observed increase in PVR, through its effect on right ventricular function, could have partly explained the CVP increase. Through the vasoconstrictor effects of 5-HT, venoconstriction could have developed, thus increasing venous return.

In contrast to the triphasic systemic pressure response to 5-HT, the pulmonary response was hypertensive. This 5-HT-induced pulmonary arterial hypertension corroborated results of other studies performed in calves,[21,38] dogs, and cats.[70,71] In the present study, although CO was also increased during 5-HT infusion, the pulmonary hypertensive response was mainly attributable to the doubling of PVR. Such an increase in PVR has been described in many species in response to 5-HT,[70,72,73] presumably reflecting an intense pulmonary vasoconstriction. These data were in agreement with those from in vitro studies in which 5-HT was a potent pulmonary vasoconstrictor in various preparations, including bovine pulmonary arteries and veins.[55,74] Moreover, the concomitant constancy of PW suggested that, in vivo, 5-HT acts primarily as a precapillary vasoconstrictor.

On the basis of the description of 5-HT-induced cardiovascular responses, we hypothetize that 5-HT could be involved in the pathophysiologic mechanisms of hypoxic pulmonary vasoconstriction, which is exceptionally prominent in the bovine species. Typing of the serotonergic receptors responsible for these responses would seem beneficial to our understanding of these effects.

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[a]Leader cath 18G, Vygon, Brussels, Belgium.
[b]Desilet 8F, Vygon, Brussels, Belgium.
[c]16G, Vygon, Brussels, Belgium.
[d]Cardiofax GEM, Nihon-Kohden, Tokyo, Japan.
[e]Bentley Trantec, model 800, ACEC, Charleroi, Belgium.
[f]HeRes, ACEC, Charleroi, Belgium.
[g]ES 1000, Viggo-Spectramed, Bilthoven, The Netherlands.
[h]Elecath 73-4067, 7F, Colombus Instruments, Colombus, Ohio.
[i]Statham P23ID, Viggo-Spectramed, Bilthoven, The Netherlands.
[j]Sirecust 302D, Siemens, Munchen, Germany.
[k]Multipurpose 7F, Cordis, Brussels, Belgium.
[l]Statham P23XL, Viggo-Spectramed, Bilthoven, The Netherlands.
[m]Cardiomax II, Colombus Instruments, Colombus, Ohio.
[n]Intraflex, Vascumed, Ghent, Belgium.
[o]Sigma Chemical Co, St Louis, Mo.
[p]960 Volumetric infusion pump, Imed Ltd, San Diego, Calif.
[q]Donatsch P, Engel G, Richardson BP, et al. ICS 205–930: a highly selective and potent antagonist at peripheral neuronal 5-hydroxytryptamine 5-HT receptors (abstr). *Br J Pharmacol* 1984;81:34P.

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