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Effects of Thoracic Epidural Anesthesia on Coronary Arteries and Arterioles in Patients with Coronary Artery Disease

Sture Blomberg, M.D., Ph.D., Håkan Emanuelsson, M.D., Ph.D.,† Henry Kvist, M.D., Ph.D.,‡ Carl Lamm, M.D.,‡ Johan Pontén, M.D., Ph.D.,§ Finn Waagstein, M.D., Ph.D.,† Sven-Erik Ricksten, M.D., Ph.D.§*

The effect of cardiac sympathetic blockade by high thoracic epidural anesthesia (TEA) (T1–T6, bupivacaine) on the luminal diameter of normal and diseased portions of epicardial coronary arteries was determined by quantitative coronary angiography in patients (n = 27) with severe coronary artery disease (CAD). In a separate group of patients (n = 9) with severe CAD, the effects of TEA on coronary arterioles (resistance vessels) were studied, by measuring total and regional myocardial blood flow and metabolism with the retrograde coronary sinus thermodilution technique. At the stenotic segments, TEA induced an increase in luminal diameter from 1.34 ± 0.11 to 1.56 ± 0.13 mm ($P < 0.002$), but did not change the diameter of the nonstenotic segments (3.07 ± 0.13 to 2.99 ± 0.13 mm). In the second group of patients, TEA induced no changes in coronary perfusion pressure, total or regional myocardial blood flow, coronary venous oxygen content, coronary blood flow distribution, regional myocardial oxygen consumption, or lactate extraction or uptake. Two patients had chest pain in the control situation and had regional myocardial lactate production that was attenuated by TEA. We conclude that TEA may increase the diameter of stenotic epicardial coronary artery segments in patients with CAD without causing a dilation of coronary arterioles. These effects may be beneficial when high TEA is used to treat severe ischemic chest pain in patients at rest. (Key words: Anesthetics, local: bupivacaine. Anesthetic techniques: thoracic epidural. Arteries, coronary: stenosis. Heart, blood flow: metabolism.)

PAIN arising from myocardial ischemia is mediated by sympathetic afferent nerves.[1] Epidural blockade of the upper thoracic sympathetic segments with local anesthetics has been shown to offer good pain relief in patients with acute myocardial infarction[2,3] or unstable angina pectoris.[4] Furthermore, thoracic epidural anesthesia (TEA) in patients with unstable angina pectoris also has beneficial effects on the major determinants of myocardial oxygen demand: it reduces heart rate (HR), preload, and afterload without affecting coronary perfusion pressure.[5]

Large coronary epicardial arteries and coronary arterioles or resistance vessels are innervated by the sympathetic nervous system.[6] Both coronary arteries and arterioles have innervated vasoconstrictor alpha-receptors, and there is considerable evidence for alpha-adrenergic regulation of large coronary arteries and coronary resistance vessels.[6,7] Studies on cardiac denervation in animals and alpha-receptor blockade in normal humans do not clearly indicate whether there is a resting sympathetic vasoconstrictor tone of the coronary circulation.[6] Furthermore, there are no data on the effect of cardiac sympathectomy by regional epidural blockade of the upper sympathetic segments on the resting coronary vascular tone in patients with coronary artery disease (CAD). This is of particular relevance, since dilation of stenotic segments of coronary arteries may be beneficial in patients with CAD, whereas dilation of coronary resistance vessels, which normally regulate myocardial blood flow, may cause redistribution of coronary blood flow and myocardial ischemia.[8]

The aim of the current investigation was therefore to determine whether cardiac sympathetic blockade with TEA affects the tone of the coronary arteries and arterioles in patients with CAD at rest. In one group of patients with severe CAD, we studied the effect of TEA on coronary blood vessel diameter in stenosed or nonstenosed epicardial blood vessels by quantitative coronary angiography. To investigate the effects of TEA on coronary arterioles we studied coronary hemodynamics before and during TEA with the retrograde coronary sinus thermodilution technique in a separate group of patients with severe CAD.

Methods

The study was approved by the Human Ethics Committee of the University of Gothenburg, and informed consent was obtained from all patients. Thirty-three patients, 31 men and 2 women, were included in the study. All patients were subjected to coronary arteriography because of severe CAD and were subsequently considered for coronary artery bypass surgery or coronary angioplasty. Previous history of cardiac disease, the severity of CAD, and the cardiac medication of the patients are described below and also are shown in tables 1 and 2.

At least 1 day prior to the investigation, a Portex® epidural catheter was inserted through a Tuohy needle *via* the second or third thoracic vertebral interspaces, by the median approach and the loss-of-resistance technique.

* Research Fellow in Anesthesia and Intensive Care.
† Associate Professor of Internal Medicine.
‡ Staff Radiologist.
§ Associate Professor of Anesthesia and Intensive Care.

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Address reprint requests to Dr. Ricksten: Department of Anesthesia and Intensive Care, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden.

TABLE 1. Clinical History, Angiographic Findings, and Medical Treatment of Patients Undergoing Quantitative Coronary Angiography

			Previous History			Coronary Angiography		Medical Treatment				
Patient Number	Sex	Age (yr)	MI	Coronary Bypass Surgery	PTCA	Main-Stem Stenosis	Number of Obstructed Vessels	Beta-adrenergic Blockers	Calcium-Channel Blockers	Long-Acting Nitrates	Salicylates	Heparin
1	M	72	1	−	−	−	3	+	+	+	−	+
2	M	65	−	−	−	−	3	+	−	−	−	−
3	M	63	−	−	−	+	3	+	−	+	+	−
4	M	73	1	−	−	−	2	+	+	+	+	−
5	M	70	2	−	−	−	3	+	+	+	−	−
6	M	67	1	−	−	−	3	+	+	+	+	−
7	M	45	1	−	−	−	2	+	+	−	−	−
8	M	48	−	−	−	−	2	+	−	−	−	−
9	F	67	1	−	−	−	3	+	−	+	−	−
10	M	69	1	−	−	−	3	+	+	+	−	−
11	M	65	3	−	−	−	3	+	+	+	−	−
12	M	63	−	−	−	+	3	+	+	+	−	−
13	M	55	−	−	−	−	1	+	+	+	−	−
14	M	70	−	−	−	−	3	+	−	+	+	−
15	M	63	−	−	−	−	2	−	−	−	−	−
16	M	50	1	−	−	−	2	+	−	+	−	−
17	M	59	−	−	−	−	2	+	+	+	−	−
18	M	61	−	−	−	−	3	+	−	+	−	−
19	F	51	−	−	−	−	3	−	+	−	+	−
20	M	71	1	−	+	−	2	+	+	+	+	−
21	M	53	1	−	−	−	1	+	−	−	−	−
22	M	73	2	−	−	−	3	+	+	+	+	−
23	M	56	2	−	−	−	3	+	+	+	−	−
24	M	69	−	−	+	−	1	+	+	+	+	+
25	M	72	−	−	−	−	2	+	+	+	+	−
26	M	74	−	+	−	−	3	+	+	+	+	+
27	M	58	1	+	−	−	3	+	+	+	+	+

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

The aim was to place the tip of the catheter at the level of the upper thoracic vertebrae. A sufficient amount of bupivacaine (5 $mg \cdot ml^{-1}$) was given to induce blockade of the cardiac sympathetic segments T1–T5. To determine the spread of anesthesia, the ability to discriminate temperature was tested 30 min after the epidural injection of bupivacaine. This individually titrated dose of bupivacaine was then given on the experimental day. The experimental procedures were performed without preanesthetic medication at 7:30 AM (coronary angiography, n = 27) or at 12:00 AM (coronary sinus blood flow [CSBF] measurements, n = 9). The patients received their ordinary cardiac medication at 6:30 AM on the experimental day. No patient received sublingual nitroglycerin on the day of investigation.

CORONARY ANGIOGRAPHY AND DETERMINATION OF CORONARY ARTERY DIAMETERS

Quantitative coronary angiography was performed in 27 patients (table 1). Fourteen patients had suffered one or more previous myocardial infarctions; 2 had undergone coronary bypass surgery; and 2 had undergone coronary angioplasty. Main-stem stenosis was present in 2 patients, and two- or three-vessel disease in 24 patients. All but 2 were taking beta-adrenergic blocking drugs; 18 were taking calcium channel blocking drugs; and 21 were taking long-acting nitrates.

Coronary artery catheterization was performed by Judkins's technique.[9] Multiple views of each coronary artery were obtained with repeated 6-ml doses of iohexol (350 $mg\ I \cdot ml^{-1}$), as contrast medium, at a flow rate of 3 $ml \cdot s^{-1}$. A conventional, 35-mm videotape angiography technique on a Siemens Angioscope at an exposure rate of 25 frames per s was used. Fluoroscopic images were simultaneously recorded on a videotape recorder, and the projection that optimally visualized the stenotic area was chosen. Unaffected vessel segments just proximal to branching were selected. The projection angle and the distance between the patient and the image intensifier was then kept constant throughout the test. The contrast medium was then injected into the diseased coronary artery without TEA (control) and with TEA (30 min after epidural injection of bupivacaine). HR and arterial blood pressure were continuously monitored.

For determination of coronary artery diameters, the angiography videotapes were reviewed on a Tagarno 35 CX projector. End-diastolic frames with adequate and comparable contrast fillings were selected from the film. The selected frames were reproduced on x-ray film and

TABLE 2. Clinical History, Angiographic Findings, and Medical Treatment of Patients Undergoing Coronary Sinus and Pulmonary Artery Catheterization

Patient Number	Sex	Age (yr)	Previous history			Coronary Angiography		Medical Treatment				
			MI	Coronary Bypass Surgery	PTCA	Main-Stem Stenosis	Number of Obstructed Vessels	Beta-Adrenergic Blockers	Calcium-Channel Blockers	Long-Acting Nitrates	Salicylates	Heparin
1	M	59	2	–	–	–	3	+	–	–	–	–
2	M	67	1	–	–	–	3	+	+	+	+	–
3	M	65	2	–	–	–	2	+	+	+	+	–
4	M	63	–	–	–	+	3	+	–	+	+	–
5	M	57	2	1	–	–	3	+	+	+	–	+
6	M	61	2	–	–	+	3	+	+	+	+	–
7	F	60	–	–	–	–	1	+	+	+	–	–
8	M	71	1	–	1	–	2	+	+	+	+	–
9	M	72	–	–	–	–	2	+	+	+	+	–

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

magnified to 1.5–2×. With this magnification it was possible to trace the opacified edges of the coronary artery lumina manually with a sharp pencil. The two x-ray images (control and TEA) of each patient were analyzed as a pair, to ensure that the images were comparable. The diameters of the stenotic and the nonstenotic arteries on the x-ray images were measured in each patient with the use of a caliper (Peak Anastigmat Lupe 4×, no. 1990) with a built-in 0.1-mm scale, by two experienced investigators who were blinded to the phase of the study and who reached consensus for each measurement. The *in vivo* coronary diameters were determined with the external diameter of the Judkin's catheter (2.7 mm) as a reference. The coefficient of variation for repeated blind determinations of coronary luminal diameter was 2.4%.

Coronary Blood Flow Measurements

Measurements of coronary and central hemodynamics were performed in nine patients (table 2). Six patients had a previous history of one or more myocardial infarctions; two patients had a main-stem stenosis; and all patients but one had a two- or three-vessel CAD. Five patients met the angiographic criteria for steal-prone coronary anatomy,[10] *i.e.*, a total occlusion of a major coronary branch with collateral flow into the bed distal to the occlusion and a proximal stenosis (>50% diameter reduction) of the artery supplying the collaterals. All patients were taking beta-adrenergic blockers; all but two were taking calcium-channel blockers; and all but one were taking long-acting nitrates. Patients 6 and 7 had chest pain at rest during the experimental procedure. Patients 2, 8, and 9 were identical to patients 6, 20, and 25 in the quantitative coronary angiography investigation.

A pulmonary artery catheter (*via* the right internal jugular vein) and a radial artery catheter were inserted for continuous recording of pulmonary and systemic arterial pressures. A coronary sinus catheter (Wilton-Webster) with four thermistors was inserted *via* the right internal jugular vein using the Seldinger technique, and was introduced into the coronary sinus and advanced to the great cardiac vein (GCV) under fluoroscopic guidance and continuous pressure monitoring. The distal mixing thermistor was placed in the GCV, and its proximal mixing thermistor was chosen to be either 2.5 or 4.5 cm from that in the GCV so that temperature changes from cold saline injections in the right atrium did not interfere with CSBF. The appropriate position of the coronary sinus catheter was confirmed by injection of 3–4 ml of contrast medium and by rapid central venous injection of cold saline during continuous flow recording. Blood was sampled from the GCV and the radial artery. GCV flow (GCVF) and CSBF were determined in duplicate. The coefficient of variation for GCVF and CSBF determinations were 5.2%.

Systolic (SAP), diastolic (DAP), and mean arterial pressures (MAP) were measured throughout the study, as were systolic (SPAP), diastolic (DPAP), mean pulmonary arterial (MPAP), pulmonary capillary wedge (PCWP), and right atrial (RAP) pressures. The systemic and pulmonary artery pressures were continuously monitored and recorded on a Mingograph 82 (Siemens-Elema, Sweden). Blood samples for lactate and oxygen content measurements were drawn simultaneously from the GCV and the radial artery. Blood oxygen saturation was determined by a photometric method (OSM 2 Hemoximeter, Radiometer, Copenhagen), and lactate concentration was assayed by an enzymatic method (Lactate Analyzer 640, Roche Bio-Electronics, Switzerland). CSBF and GCVF were determined in duplicate by the retrograde thermodilution technique originally described by Ganz *et al.*[11] and modified by Pepine *et al.*[12] Normal saline at room temperature was used as the indicator and was injected at 40 $ml \cdot min^{-1}$ over approximately 20 s for each measurement. Changes in thermistor resistances due to temperature changes were measured with a Wheatstone

bridge and were recorded on a Mingograph 82. Blood drawn from the GCV represents left anterior descending artery perfusion.

Cardiac index (CI, $l \cdot min^{-1} \cdot m^{-2}$), stroke volume index (SVI, $ml \cdot m^{-2}$), systemic (SVR) and pulmonary vascular (PVR) resistances ($mmHg \cdot min \cdot l^{-1}$) and systemic (SVRI) and pulmonary (PVRI) vascular resistance indices ($mmHg \cdot min \cdot m^2 \cdot l^{-1}$), regional (GCV) myocardial oxygen consumption ($RM\dot{V}_{O_2}$, $ml \cdot min^{-1}$), oxygen content (GCV_{O_2}, $ml \cdot 100\ ml^{-1}$), lactate extraction (per cent) and lactate uptake ($\mu mol \cdot min^{-1}$) were calculated with standard formulas. Hemodynamic measurements were performed, and blood samples were obtained with patients in the supine position, at rest without TEA (control) and 20–30 min after the epidural injection of bupivacaine 5 $mg \cdot ml^{-1}$ (TEA).

Data were analyzed with a paired Student's t test. P values < 005 were considered statistically significant.

Results

Dosage, Spread and Duration of Epidural Bupivacaine

An average amount of 3.8 ± 0.2 ml of bupivacaine (5 $mg \cdot ml^{-1}$) induced a blockade of the upper thoracic segments with a mean rostral spread to T1.2 ± 0.2 and a mean caudal spread to T6.2 ± 0.2. The mean duration of the anesthesia was 95 ± 6 min.

Effects of TEA on Large Coronary Dimensions

Seventeen left anterior descending, 6 circumflex, and 3 right coronary arteries with significantly stenosed segments (57 ± 3%, range 35–90%) were studied. The individual changes in the diameter of the stenotic (n = 26) and nonstenotic (n = 27) segments are shown in table 3. TEA caused a significant increase of the diameter of the stenotic segments, from 1.34 ± 0.11 to 1.56 ± 0.13 mm ($P < 0.002$) (fig. 1), whereas there was no change in the diameter of the nonstenosed coronary arteries (3.07 ± 0.13 to 2.99 ± 0.13 mm). HR decreased significantly, from 60 ± 2 to 57 ± 2 beats per min ($P < 0.05$) but there were no significant changes in SAP (139 ± 5 to 136 ± 5 mmHg) or DAP (73 ± 3 to 71 ± 2 mmHg).

Effects of TEA on Central Hemodynamics, Coronary Blood Flow and Myocardial Metabolism

TEA had no effects on the central hemodynamic variables studied (table 4). Furthermore, there were no significant changes in coronary hemodynamics or myocardial metabolism (table 5).

Two patients (6 and 7) had chest pain at rest and had regional myocardial lactate production. In these patients, TEA induced complete analgesia that was associated with less pronounced regional myocardial lactate production. Their respective values of RMLE increased from −41.7 to −4.5% and from −20.7 to −10.9% during TEA.

Discussion

When assessing the effects of cardiac sympathetic blockade by TEA on the coronary circulation, it is important to distinguish between epicardial coronary arteries and intramyocardial coronary arterioles or resistance vessels. Not only do these vessels differ in structure and function, but also they may respond differently to the same vasoactive stimulus.[13–15] Coronary arterioles or resistance vessels regulate coronary blood flow and its distribution according to demand, through local metabolic control.[6] Epicardial coronary arteries, in contrast, normally contribute little to the regulation of coronary blood flow,[16] but undergo active vasodilation and vasoconstriction in response to a variety of autonomic and pharmacologic stimuli.[7] This coronary artery vasomotion is of importance in CAD, since approximately 75% of arteriosclerotic coronary stenoses behave in a dynamic but not in a fixed fashion.[17,18]

The epicardial coronary arteries as well as the coronary arterioles are densely innervated with sympathetic adrenergic nerve fibers.[6,19] In animals it has been demonstrated that epicardial coronary arteries constrict during cardiac sympathetic or alpha-receptor stimulation.[6,20] It has also been demonstrated in humans that activation of the sympathetic nervous system by sustained isometric hand-grip or cold pressor test constricts luminal area in normal and diseased coronary segments.[21,22] Cardiac sympathetic stimulation causes an alpha-receptor-mediated coronary vasoconstrictor influence on the coronary arterioles or resistance vessels; this influence limits the local metabolic vasodilation and results in a decreased coronary sinus oxygen tension both in animals and in patients with CAD.[6,23–26] Furthermore, in the presence of experimentally produced coronary artery stenosis or adenosine-induced maximal coronary artery dilatation, adrenergic stimulation may induce coronary vasoconstriction.[26,27] However, data from denervation studies in dogs and in humans do not clearly indicate whether there is a resting sympathetic vasoconstrictor tone of the coronary circulation during normal conditions.[6]

In contrast, during experimental myocardial ischemia, it has been shown that cardiac sympathectomy by TEA may improve regional myocardial blood flow distribution by increasing the endocardial-to-epicardial blood flow ratio.[28,29] Furthermore, Reiz *et al.*[30] showed in four patients with CAD that coronary vascular resistance was reduced with TEA, although TEA also induced an extensive blockade (T1–T12) with a pronounced decrease in blood pressure. In that situation, coronary vasodilation might well be an autoregulatory response to a decrease in per-

TABLE 3. Individual Data on the Effects of TEA on Hemodynamics and Dimensions of Stenosed and Nonstenosed Coronary Arteries

Patient Number	SAP (mmHg)		DAP (mmHg)		HR (beats per min)		Diameter of Stenosed Segments (mm)		Diameter of Nonstenosed Segments (mm)	
	C	TEA	C	TEA	C	TEA	C	TEA	C	TEA
1	120	110	50	50	62	58	1.85	2.38	3.17	3.17
2	123	120	68	68	63	61	0.84	1.50	4.07	3.47
3	174	165	86	77	58	56	1.44	1.86	2.51	3.17
4	130	128	64	63	50	48	1.24	1.73	2.27	2.54
5	115	112	54	60	58	52	1.21	1.09	2.30	2.13
6	202	183	100	98	44	40	0.76	1.08	2.92	3.30
7	107	100	67	63	50	45	2.84	3.31	3.92	3.65
8	116	113	66	69	57	56	0.92	1.17	3.87	3.56
9	130	127	72	65	51	47	1.27	0.82	3.65	3.76
10	120	130	65	65	55	55	1.60	1.47	4.42	3.74
11	115	110	75	60	59	55	—	—	2.46	2.57
12	153	122	71	83	71	64	1.21	1.09	2.70	2.41
13	133	148	72	83	60	69	0.68	0.74	2.57	2.03
14	175	180	90	68	54	46	1.41	1.41	2.69	2.63
15	153	137	90	80	82	73	0.88	1.22	3.58	4.05
16	111	117	79	79	54	54	0.95	0.95	2.36	1.89
17	167	150	100	93	55	51	0.25	0.44	3.02	2.96
18	157	127	73	63	62	53	1.57	2.14	2.70	2.77
19	153	163	80	80	68	59	1.13	1.32	3.77	4.03
20	153	159	57	63	57	62	1.43	1.47	3.05	3.02
21	168	155	84	79	60	57	1.13	1.19	3.02	2.96
22	125	126	70	69	73	68	1.20	1.86	3.53	3.59
23	124	120	77	75	70	64	1.96	2.03	2.70	2.36
24	163	129	81	63	83	54	1.94	1.71	2.06	1.88
25	145	140	70	68	60	57	1.90	2.70	3.68	3.68
26	106	170	54	68	56	73	1.57	1.73	2.65	2.43
27	115	122	65	65	66	63	1.84	2.16	3.19	3.03

SAP = systolic blood pressure; DAP = diastolic blood pressure; HR = heart rate; C = control values; TEA = thoracic epidural anesthesia.

fusion pressure and might not necessarily be caused by a reduced sympathetic stimulation of the coronary vessels.[31] No study has yet appeared on the effects of regional cardiac sympathetic blockade by high TEA on resting constrictor tone of coronary arterioles or on the diameters of stenosed or nonstenosed epicardial coronary arteries in patients with CAD.

In the current study, quantitative coronary angiography was therefore performed with and without TEA to investigate the effects of TEA on the diameters of epicardial coronary vessels in 27 patients with severe CAD. TEA caused a highly significant increase in the diameter of the stenotic segments, but no effects on the nonstenotic segments. Since approximately 75% of coronary stenoses are dynamic, one would expect that approximately 25% of the patients would have had fixed stenoses not responding to TEA. As can be seen from table 3, 10 of the patients (38%) either demonstrated a decrease or a minimal increase in diameter. The contrast medium used, iohexol, has been shown to have a small dilatory influence on coronary arteries that disappears within 2 min and may therefore not have interfered with the effect of TEA 20–30 min later.[32] In the current study, as well as in other studies using computerized quantitative angiography,[33,34] the crucial point is to define the luminal border of the vessel. However, it is likely that our results are valid, since the coefficient of variation for the determination of coronary luminal diameter was low, and since we used a carefully blinded protocol.

What, then, are the mechanisms behind the dilating effects of TEA on the coronary stenotic segments? It is not likely to be caused by a TEA-induced change in coronary perfusion pressure, since arterial blood pressure and PCWP were unchanged by TEA. Stimulation of beta-adrenoceptors ($beta_1$ and $beta_2$) and alpha-adrenoceptors ($alpha_1$ and $alpha_2$) may cause dilatation and constriction, respectively, of coronary arteries.[7] The relaxing effects of beta-adrenergic agonists and the contractile effects of alpha-adrenergic agonists are reduced and enhanced, respectively, after experimental removal of the endothelium.[35–37] In patients with CAD, it has been shown that acetylcholine, which in normal arteries promotes the release of endothelium-derived relaxing factor, induces a constriction of arteriosclerotic coronary arteries, which is suggestive of a defect in endothelial vasodilator function in diseased coronary arteries.[38] It has been demonstrated also that adrenergic nerves of coronary arteries with experimentally induced endothelial damage may accumulate 5-hydroxytryptamine released from aggregating platelets. 5-hydroxytryptamine may then act as a "false neurotransmitter" and cause a coronary vasoconstriction upon adrenergic nerve stimulation.[39,40] Furthermore, almost

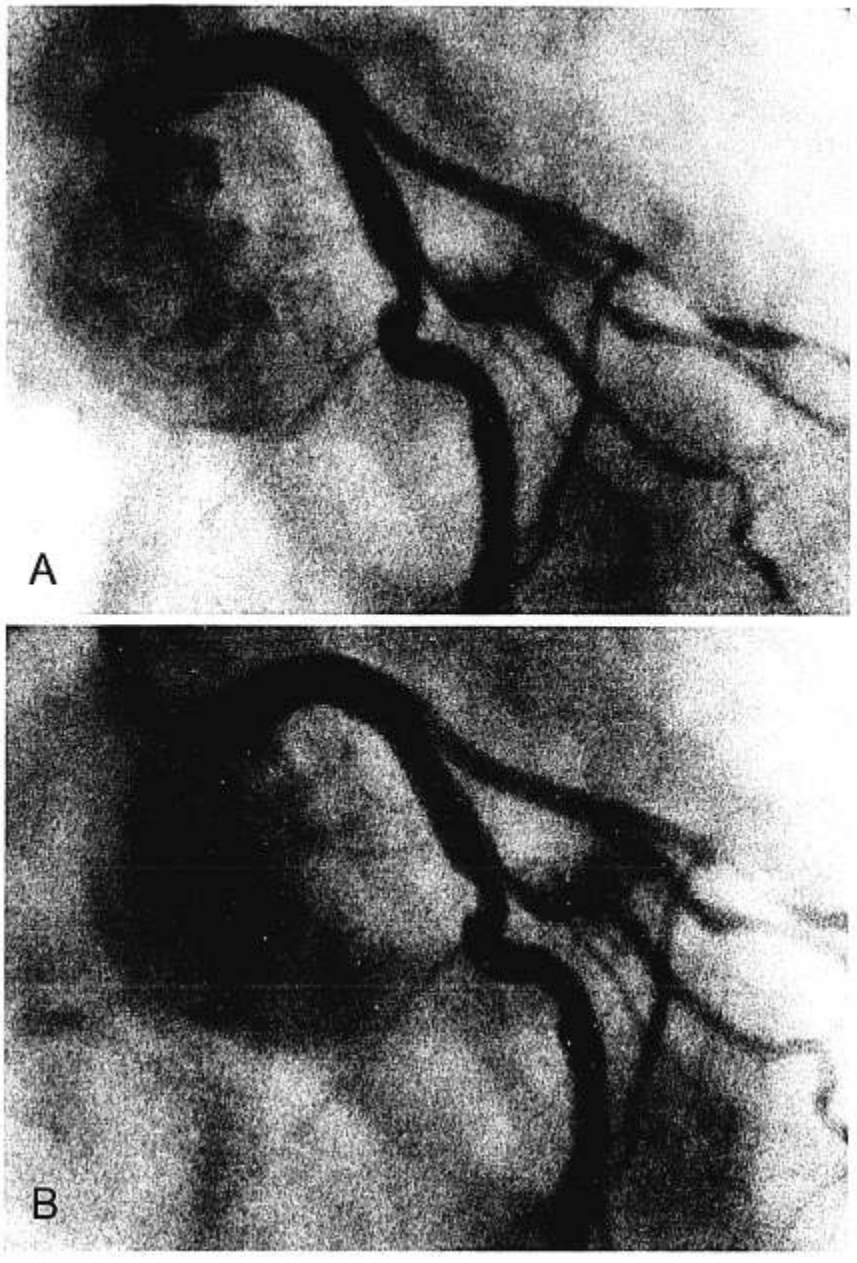

FIG. 1. A stenosed circumflex artery (patient 18, see tables 1 and 3) before (*A*) and after (*B*) thoracic epidural anesthesia. The diameter of the stenosis increased from 1.57 mm to 2.14 mm (see table 3).

all patients in the current study were undergoing treatment with beta-adrenergic blockers. Studies have suggested that beta-adrenergic blockers cause a direct constriction of coronary arteries by unmasking the effect of postjunctional alpha-adrenoceptors.[41,42] The combination of beta-adrenergic blockers and withdrawal of cardiac sympathetic alpha-constrictor tone by TEA may therefore have revealed, in the arteriosclerotic epicardial coronary arteries with a damaged endothelium, a resting sympathetic vasoconstrictor tone that was not seen in nonstenotic segments of coronary arteries with an intact endothelium.

We could not demonstrate any effects of regional cardiac sympathetic blockade on $RM\dot{V}_{O_2}$, most likely because three of the four major determinants of myocardial oxygen demand (HR, SAP, and PCWP) were not significantly altered by TEA. Myocardial contractility was not measured, but it is less likely that this variable was affected by TEA, since all patients were undergoing beta-adrenergic blockers treatment, which probably also explains the lack of heart decline. We have previously shown that TEA may decrease HR in patients treated with beta-adrenergic blockers if there is a high, prevailing cardiac sympathetic tone, such as that during anginal pain[4,5] or dynamic exercise.[4] However, it also has been demonstrated that during basal conditions, *i.e.*, during rest without ischemic chest pain, TEA did not change HR, SAP

or PCWP[5]; these data are confirmed by the current study. Therefore, depending on the prevailing cardiac sympathetic tone, high TEA may cause a greater or lesser number or changes in central hemodynamics in patients with CAD who are being treated with beta-adrenergic blockers.

Regional cardiac sympathetic blockade caused no changes in coronary perfusion pressure, myocardial blood flow, or coronary venous oxygen content, indicating a lack of effect on coronary resistance vessels. Changes in the GCVF/CSBF ratio concomitant with coronary vasodilation, as reflected by a reduced myocardial oxygen extraction, has been used to indicate maldistribution of coronary blood flow (coronary steal) during isoflurane anesthesia.[43,44] Coronary steal is recognized as a cause of myocardial ischemia only in patients with the anatomic basis for steal. Although five of the nine patients in the current study demonstrated steal-prone coronary anatomy, TEA did not cause small-vessel coronary vasodilation, change in the GCVF/CSBF ratio, or regional myocardial ischemia. However, the lack of change of the GCVF/CSBF ratio cannot rule out the possibility that coronary blood flow maldistribution is present. Furthermore, the retrograde coronary sinus thermodilution technique cannot be used to reveal transmural flow maldistribution.

We have previously demonstrated that induction of TEA in patients with unstable angina and ischemic chest pain causes a decrease in the major determinants of myocardial oxygen demand, accompanied in some patients by less pronounced ST-segment depression.[5] Also, the current study showed that TEA improved the myocardial oxygen supply/demand ratio, as evidenced by a TEA-induced improvement of lactate metabolism in two patients with lactate production and angina at rest. In these two patients, afterload and $RM\dot{V}_{O_2}$ decreased somewhat (although HR and PCWP were unaffected), which may explain the improvement in lactate metabolism. However, it is tempting to speculate that TEA also may improve regional perfusion of ischemic areas by increasing the luminal diameter of stenotic arteries; however, this hypothesis remains to be proven.

In the current study on patients with severe CAD, we have shown that regional cardiac sympathetic blockade with high TEA significantly increases the diameter of stenotic but has no effect on nonstenotic epicardial coronary artery segments. Furthermore, cardiac sympathetic blockade with TEA in these patients does not cause a small-vessel coronary vasodilation. TEA-induced dilation of stenotic segments of large coronary arteries without causing any changes in the tone of the coronary resistance vessels may be valuable when TEA is used to control pain in patients with CAD and unstable angina with severe chest pain at rest.

TABLE 4. Effects of TEA on Central Hemodynamics

	Control	TEA	
SAP (mmHg)	170 ± 9	159 ± 10	NS
MAP (mmHg)	109 ± 6	102 ± 5	NS
DAP (mmHg)	79 ± 5	74 ± 4	NS
SPAP (mmHg)	28 ± 1	27 ± 2	NS
MPAP (mmHg)	16 ± 1	16 ± 2	NS
DPAP (mmHg)	9 ± 1	9 ± 1	NS
PCWP (mmHg)	8 ± 1	7 ± 1	NS
CVP (mmHg)	4 ± 1	3 ± 2	NS
CO ($l \cdot min^{-1}$)	5.1 ± 0.5	4.9 ± 0.4	NS
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.6 ± 0.2	2.4 ± 0.2	NS
HR ($beats \cdot min^{-1}$)	60 ± 4	61 ± 4	NS
SV ($ml \cdot beat^{-1}$)	87 ± 8	81 ± 7	NS
SVI ($ml \cdot beat^{-1} \cdot m^{-2}$)	43 ± 3	40 ± 3	NS
SVR ($mmHg \cdot min \cdot l^{-1}$)	21.1 ± 1.4	21.3 ± 1.5	NS
SVRI ($mmHg \cdot min \cdot l^{-1} \cdot m^2$)	42 ± 3	42.4 ± 2.8	NS
PVR ($mmHg \cdot min \cdot l^{-1}$)	1.7 ± 0.2	1.8 ± 0.2	NS
PVRI ($mmHg \cdot min \cdot l^{-1} \cdot m^2$)	3.2 ± 0.2	3.6 ± 0.4	NS

Values are means ± SEM.

SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure; SPAP = systolic pulmonary arterial pressure; MPAP = mean pulmonary arterial pressure; DPAP = diastolic pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CO = cardiac output; CI = cardiac index; HR = heart rate; SV = stroke volume; SVI = stroke volume index; SVR = systemic vascular resistance; SVRI = systemic vascular resistance index; PVR = pulmonary vascular resistance; PVRI = pulmonary vascular resistance index.

TABLE 5. Effects of TEA on Coronary Hemodynamics and Metabolism

	Control	TEA	
CPP (mmHg)	72 ± 5	67 ± 4	NS
CSBF ($ml \cdot min^{-1}$)	153 ± 21	138 ± 24	NS
GCVF ($ml \cdot min^{-1}$)	76 ± 14	68 ± 14	NS
GCVF/CSF (%)	0.46 ± 0.09	0.49 ± 0.06	NS
GCV_{O_2} ($ml \cdot 100\ ml^{-1}$)	41.3 ± 4.7	39.8 ± 4.9	NS
$RM\dot{V}_{O_2}$ ($ml \cdot min^{-1}$)	9.6 ± 1.9	9.3 ± 2.0	NS
RMLE (%)	15.2 ± 9.1	12.8 ± 5.2	NS
RMLU ($\mu mol \cdot min^{-1}$)	7.6 ± 3.6	4.9 ± 1.8	NS

Values are means ± SEM.

CSBF = coronary sinus blood flow; CPP = coronary perfusion pressure; GCVF = great cardiac vein flow; GCV_{O_2} = great cardiac vein oxygen content; $RM\dot{V}_{O_2}$ = regional myocardial oxygen consumption; RMLE = regional myocardial lactate extraction; RMLU = regional myocardial lactate uptake.

References

1. Bishop VS, Malliani A, Thorén P: Cardiac mechanoreceptors, Handbook of Physiology: The Cardiovascular System III. Edited by Shepherd JT, Abboud FM. Baltimore, William and Wilkins, 1983, pp 497–555
2. Tevelenok YUA: Peridural anesthesia in the acute period of myocardial infarction. Anesteziol Reanimatol 3:36–39, 1977
3. Toft P, Jörgensen A: Continuous thoracic epidural analgesia for the control of pain in myocardial infarction. Intensive Care Med 13:388–389, 1987
4. Blomberg S, Curelaru I, Emanuelsson H, Herlitz J, Pontén J, Ricksten S-E: Thoracic epidural anaesthesia in patients with unstable angina pectoris. Eur Heart J 10:437–444, 1989
5. Blomberg S, Emanuelsson H, Ricksten S-E: Thoracic epidural anesthesia and central hemodynamics in patients with unstable angina pectoris. Anesth Analg 69:558–562, 1989
6. Feigl ED: Coronary physiology. Physiol Rev 63:1–205, 1983

7. Young MA, Vatner SF: Regulation of large coronary arteries. Circ Res 59:579–596, 1986
8. Becker LC: Conditions for vasodilator induced coronary steal in experimental myocardial ischemia. Circ Res 57:1103–1110, 1978
9. Judkins MP: Selective coronary arteriography: A percutaneous transfemoral technique. Radiology 89:815–819, 1967
10. Buffington CW, Davis KB, Gillespie S, Pettinger M: The prevalence of steal-prone coronary anatomy in patients with coronary artery disease: An analysis of the coronary artery surgery study registry. ANESTHESIOLOGY 69:721–727, 1988
11. Ganz W, Tamura K, Marcus HS, Conoso R, Yoshuda S, Swan HJG: Measurements of coronary sinus blood flow by continuous thermodilution in man. Circulation 44:181–195, 1971
12. Pepine CJ, Metha J, Webster WW, Jr, Nicholas WW: In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary artery disease. Circulation 58:795–802, 1978
13. Feldman RL, Hill JA, Conti JB, Conti CR, Pepine CJ: Analysis of coronary responses to nifedipine alone and in combination with intracoronary nitroglycerin in patients with coronary artery disease. Am Heart J 105:651–658, 1983
14. Wilkowski DAW, Sill JC, Bonta W, Owen R, Bove AA: Nitrous oxide constricts epicardial coronary arteries without effect on coronary arterioles. ANESTHESIOLOGY 66:659–665, 1987
15. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C: Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. ANESTHESIOLOGY 66:277–279, 1987
16. Epstein SE, Cannon RO, Talbot TL: Hemodynamic principles in the control of coronary blood flow. Am J Cardiology 56:4E–10E, 1985
17. Gould KL: Dynamic coronary stenosis. Am J Cardiol 45:286–292, 1980
18. Brown BG: Coronary vasospasm: Observations linking the clinical spectrum of ischemic heart disease to the dynamic pathology of coronary artery atherosclerosis. Arch Intern Med 141:716–722, 1981
19. Denn MJ, Stone HL: Autonomic innervation of dog coronary arteries. J Appl Physiol 41:30–35, 1976
20. Vatner SF, Pagani M, Manders WT, Pasipoularides AD: Alpha adrenergic vasoconstriction and nitroglycerin vasodilation of large coronary arteries in the conscious dog. J Clin Invest 65: 5–14, 1980
21. Brown BG: Response of normal and diseased epicardial coronary arteries to vasoactive drugs: Quantitative arteriographic studies. Am J Cardiol 56:23E–29F, 1985
22. Raizner AE, Chahine RA, Isahimori T, Verani MS, Zacca N, Jamal N, Miller RR, Luchi RJ: Provocation of coronary artery spasm by the cold pressor test: Hemodynamic, arteriographic and quantitative angiographic observations. Circulation 62:925–932, 1980
23. Brown BG, Josephson MA, Peterson RB, Pierce CD, Wong M, Hecht HS, Bolson E, Dodge HT: Intravenous dipyridamole combined with isometric handgrip for near-maximal acute increase in coronary flow in patients with coronary artery disease. Am J Cardiol 48:1077–1085, 1981
24. Kiowitz C, Parmley WW, Donoso R, Marcus H, Ganz W, Swan HJC: Effects of isometric exercise on cardiac performance: The grip test. Circulation 44:994–1002, 1971
25. Mudge GH, Jr, Grossman W, Mills RM, Jr, Lesch M, Braunwald E: Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N Engl J Med 295:1333–1337, 1976
26. Buffington CW, Feigl EO: Adrenergic coronary vasoconstriction in the presence of coronary stenosis in the dog. Circ Res 48: 416–423, 1981
27. Johanssen UJ, Mark AL, Marcus ML: Responsiveness to coronary sympathetic nerve stimulation during maximal coronary dilatation produced by adenosine. Circ Res 50:510–517, 1982
28. Davis RF, DeBoer LWV, Maroko PR: Thoracic epidural anesthesia reduces myocardial infarct size after coronary artery occlusion in dogs. Anesth Analg 65:711–717, 1986
29. Klassen GA, Bramwell RS, Bromage PR, Zborowska-Sluis DT: The effect of acute sympathectomy by epidural anesthesia on the canine coronary circulation. ANESTHESIOLOGY 52:8–15, 1980
30. Reiz S, Nath S, Rais O: The effects of thoracic epidural block and prenalterol on coronary vascular resistance and myocardial metabolism in patients with coronary artery disease. Acta Anaesthesiol Scand 24:11–16, 1980
31. Marcus ML: Autoregulation in the coronary circulation in health and disease. New York, McGraw-Hill, 1983, pp 93–112
32. Emanuelsson H, Holmberg S, Selin K, Waagstein F: Effects of iohexol and metrizoate on myocardial blood flow and metabolism. Acta Radiol Suppl (Stockh) 366, 1983
33. Gensini GG, Kelly AE, Da Costa BCB, Huntington PP: Quantitative angiography: The measurement of coronary vasomobility in the intact animal and man. Chest 60:522–530, 1971
34. Brown BG, Bolson EL, Frimer M, Dodge HT: Quantitative coronary arteriography: Estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary lesions using the arteriogram and digital computation. Circulation 55:329–337, 1977
35. Cocke TM, Angus JA: Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature 305:627–630, 1983.
36. Miller VM, Vanhoutte PM: Muscular and endothelial responsiveness to alpha-adrenergic activation in canine blood vessels. Physiologist 27:282–286, 1984
37. Rubangi GM, Vanhoutte PM: Endothelium removal decreases relaxations of coronary arteries caused by beta adrenergic agonists and adenosine. J Cardiovasc Pharmacol 7:139–144, 1985
38. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz R: Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic arteries. N Engl J Med 315: 1046–1051, 1986
39. Cohen RA: Platelet-induced neurogenic coronary arterial contractions due to accumulation of the false neurotransmitter 5-hydroxytryptamine. J Clin Invest 75:286–292, 1985
40. Cohen RA, Zitnay KM, Weisbrod RM: Accumulation of 5-hydroxytryptamine leads to dysfunction of adrenergic nerves in canine coronary artery following intimal damage in vivo. Circ Res 61:829–833, 1987
41. Brown BG: Response of normal and diseased epicardial coronary arteries to vasoactive drugs: Quantitative arteriographic studies. Am J Cardiol 56:23E–29E, 1985
42. Turlapaty PDMV, Altura BM: Propranolol induces contractions of canine small and large coronary arteries. Basic Res Cardiol 77:68–81, 1982
43. Reiz S, Östman M: Regional coronary hemodynamics during isoflurane–nitrous oxide anesthesia in patients with ischemic heart disease. Anesth Analg 64:570–576, 1985
44. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D: Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 67:936–942, 1988