Effects of High Thoracic Epidural Analgesia on Myocardial Blood Flow in Patients With Ischemic Heart Disease

Eigil Nygård, MD; Klaus F. Kofoed, MD, DMSc; Jacob Freiberg, MD, BS; Søren Holm, PhD; Jan Aldershvile, MD, DMSc†; Kirsten Eliasen, MD; Henning Kelbaek, MD, DMSc

Background—In patients with ischemic heart disease, high thoracic epidural analgesia (TEA) has been proposed to improve abnormalities of coronary function by inhibiting cardiac sympathetic tone. We evaluated the effect of TEA on myocardial blood flow in patients with ischemic heart disease.

Methods and Results—Twenty male patients with multivessel ischemic heart disease were studied. An epidural catheter was inserted between the second and third thoracic vertebral interspace (Th2 to Th3). Analgesia was induced by epidural injection of bupivacaine 0.5%, and a sensory block from the sixth cervical (C6 to C7) to Th10 (Th8 to Th11) vertebral interspace was achieved. Myocardial blood flow was measured with dynamic $^{13}$N-ammonia PET with and without TEA at rest, during pharmacological vasodilation with dipyridamole, and during sympathetic stimulation with the cold pressor test. Myocardial blood flow during dipyridamole increased similarly, regardless of TEA, in all regions except in myocardium subtended by collateral arteries in which blood flow increased more with than without TEA ($P<0.05$).

Without TEA, myocardial blood flow during the cold pressor test remained unchanged compared with myocardial blood flow at rest. In contrast, with TEA, myocardial blood flow increased in all vascular territories. Coronary vascular resistance increased during the cold pressor test without TEA, whereas with TEA, coronary resistance decreased in myocardium subtended by nonstenotic and stenotic coronary vessels and remained unchanged in myocardium subtended by occluded vessels.

Conclusions—In patients with multivessel ischemic heart disease, TEA partly normalizes the myocardial blood flow response to sympathetic stimulation. (Circulation. 2005;111:2165-2170.)

Key Words: blood flow, myocardial ischemia, myocardial analgesia, epidural

Coronary blood flow is regulated primarily by local metabolic factors; those factors, however, may be competitively or complementarily modified by cardiac neural control. Impaired myocardial sympathetic innervation as in diabetic autonomic neuropathy or in the transplanted heart is associated with a reduced coronary vasodilatory response to sympathetic stimulation, whereas sympathetic reinnervation of the transplanted heart is associated with a normal coronary vasodilatory response. In patients with coronary atherosclerosis and endothelial dysfunction, an abnormally augmented response to coronary $\alpha$-adrenergic activation has been shown to result in a reduced coronary blood flow response during sympathetic stimulation. This phenomenon is believed to reflect a disturbance of the balance between coronary endothelial vasodilatory function and vasoconstrictor effects of myocardial sympathetic tone. Inhibition of the cardiac sympathetic nerve innervation in such patients might therefore alleviate abnormalities of coronary function.

Inhibition of the sympathetic nervous outflow to the heart may be achieved by high thoracic epidural analgesia (TEA). During TEA, cardiac noradrenalin spillover decreases and thoracic cutaneous blood flow increases consistently with regional inhibition of the sympathetic tone. In patients with ischemic heart disease, TEA has been evaluated as an adjunctive treatment for refractory chest pain during stable and unstable angina pectoris and for improving postsurgical recovery after CABG. On the other hand, it remains unclear to what extent these apparently beneficial effects of TEA are mediated by changes in myocardial blood flow or whether they are merely the result of improved pain relief.

Myocardial blood flow can be evaluated noninvasively with PET. The effects of TEA on myocardial blood flow during sympathetic stimulation and pharmacological vasodilation may therefore be evaluated in patients with ischemic heart disease.

The aim of the present study was to investigate whether abnormalities of coronary function observed in patients with ischemic heart disease can be alleviated by TEA.
Methods

Study Population
Twenty male patients 67 years of age (range, 50 to 78 years) with multivessel coronary artery disease and preserved left ventricular ejection fraction scheduled for elective CABG were included. Thirteen patients had previously had an acute myocardial infarction; 10 patients were treated for arterial hypertension, and 3 patients were treated for type 2 diabetes mellitus. All patients had stable angina pectoris and underwent CABG during TEA except one patient in whom the epidural catheter was accidentally withdrawn before surgery.

The protocol was approved by the Scientific Ethics Committee for Copenhagen and Frederiksberg (KF 02-12498), and all patients gave written consent to participate in the study.

Study Protocol
On 2 consecutive days, myocardial blood flow was measured with (day 1) and without (day 2) TEA using PET; surgery was scheduled for day 3. For radiation safety and logistical reasons, patients were randomly allocated to 2 separate groups: a dipyridamole group (n=10), in which myocardial blood flow was measured at rest and during dipyridamole-induced hyperemia, and a cold pressor test group (n=10), studied at rest and during cold exposure. All patients refrained from caffeine-containing food and beverages 12 hours before the PET study, but all medications except diuretics were continued during the protocol. In patients undergoing CABG during TEA, perioperative and postoperative data, in addition to 2-year postsurgical cardiac event rate and survival, were recorded.

TEA Procedure
An 18-gauge Portex epidural catheter (Sims Portex Ltd) was inserted 3 to 4 cm into the epidural space through a Tuohy needle (Sims Portex Ltd) via the second or third thoracic (T2h to T3h) vertebral interspace. A bolus dose of 3 mL of 0.5% bupivacaine (Maracaine, Astra) was given epidurally, and 5 mg/h bupivacaine was administered to maintain a sensory blockade corresponding to at least Th1 to T8/5 assessed by regional loss of cold sensation of the corresponding dermatoms. Sensory blockade of the patients during TEA extended from C6 (C6 to C7) to T8h (T8h to Th11). Myocardial blood flow measurements were performed 15 minutes after induction of sensory blockade.

PET Studies
Myocardial blood flow was measured with a GE Medical Systems tomograph model ADVANCE as previously described.17 In brief, 13N-ammonia (700 MBq) was injected intravenously at rest, and dynamic image acquisition was performed for a total scan duration of 20 minutes. After a 35-minute interval for physical decay of the tracer, a second 13N-ammonia dose injection was injected intravenously during stress (dipyridamole or cold exposure). In the dipyridamole group, dipyridamole (0.56 mg/kg) was infused over 4 minutes, and imaging was initiated 3 minutes later. The cold pressor test group was performed by immersion of the patient’s hand and forearm 3 minutes, and imaging was initiated 3 minutes later. The cold pressor test was performed by immersion of the patient’s hand and forearm into ice water for 180 seconds as previously described.18 Heart rate, blood pressure, rate-pressure product, and mean arterial blood pressure were recorded at rest and during stress imaging.

The transaxial images were reconstructed into a zoomed 128×128 image matrix centered over the heart with a pixel size of 4.2 mm using a Hanning filter with a cutoff of 6 mm. The reconstructed and decay-corrected transaxial PET images were reoriented into 6 short-axis slices encompassing the left ventricle. On the last frames of the 13NH3 images, 16 regions of interest were semiautomatically assigned to the myocardium.17 A small region of interest in the center of the left atrium was used to derive the arterial input function. The regions were then copied to the dynamic imaging sequence to obtain time-activity curves. Tissue curves were corrected for partial volume effect, assuming a uniform myocardial thickness of 10 mm using a recovery correction coefficient of 0.81 as determined in phantom studies. Myocardial blood flow was quantified by use of a 2-compartment model and was considered nonevaluable if the input to tissue spillover fraction was >80%. Because basal myocardial blood flow at rest is related to the rate-pressure product, an index of myocardial oxygen consumption, resting blood flow values may be normalized to the corresponding rate-pressure product in each patient by dividing the resting flow value by the rate-pressure product multiplied by 10,000 in each individual patient. Myocardial blood flow at rest not normalized to the rate-pressure product is reported unless otherwise stated. Coronary vascular resistance was calculated as mean arterial pressure divided by myocardial blood flow. Image analysis was performed by an operator unaware of the study sequence.

Coronary Angiography
Classification of the coronary angiograms was performed by an experienced interventional cardiologist blinded to the results of the PET data. Myocardial segments evaluated by PET were classified as being subtended by a nonstenotic (0% to 49% luminal stenosis), a stenotic (50% to 99% luminal stenosis), or an occluded coronary artery (100% luminal stenosis) according to the principles developed by Pierard et al.18 The class of myocardial segment was determined in each patient by integrating coronary angiogram and myocardial PET flow data. Particular care was taken to minimize overlap between myocardial segment classes (nonstenotic, stenotic, and occluded) and to minimize double representation.

Statistical Analysis
Results are presented as mean±SD. A paired Student t test was used for comparisons within individuals. A randomization test was used in case of nonnormal distribution of data. A value of P<0.05 defined the level of statistical significance.

Results

Hemodynamic Data
At rest (n=20), TEA resulted in a 4% decrease in heart rate (P<0.05), whereas systolic and mean arterial blood pressures remained unchanged. An 8% decrease in the rate-pressure product was recorded during TEA (P<0.05).

Hemodynamic changes with and without TEA during dipyridamole and cold pressor test are given in Tables 1 and 2. Heart rate increased similarly during infusion of dipyridamole without and with TEA (19±7% versus 18±13%; P=NS), and mean arterial blood pressure remained unchanged.

Systolic blood pressure and rate-pressure product increased less during the cold pressor test with TEA compared to without TEA (13±11% versus 26±8% and 35±29% versus 65±33%; P<0.05).

Myocardial Blood Flow at Rest
Compared to without TEA, myocardial blood flow at rest with TEA changed <10% (n=20) both with and without

<table>
<thead>
<tr>
<th>TABLE 1. Hemodynamic Data for Dipyridamole Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without TEA</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
</tr>
</tbody>
</table>

n=10. Values are mean±SD. *P<0.005 vs rest without TEA.
corrections for changes of cardiac work by the rate-pressure product (data not shown).

**Myocardial Blood Flow Response to Dipyridamole**
After dipyridamole stimulation, myocardial blood flow increased compared with myocardial blood flow at rest in all vascular territories without and with TEA (Table 3 and Figure 1A). In myocardium subtended by occluded coronary arteries, the percentage increase in blood flow during dipyridamole compared with myocardial blood flow at rest was higher with than without TEA (P < 0.05) (Figure 2, top). Coronary vascular resistance decreased during dipyridamole in all parts of the myocardium without or with TEA (Table 4).

**Myocardial Blood Flow Response to the Cold Pressor Test**
Without TEA, myocardial blood flow during the cold pressor test remained unchanged compared with myocardial blood flow at rest (Table 3 and Figure 1B). In contrast, with TEA, myocardial blood flow increased during the cold pressor test in all vascular territories (Figures 1B and 2).

Coronary vascular resistance increased during the cold pressor test in all vascular territories without TEA; with TEA, however, vascular resistance decreased in myocardium subtended by nonstenotic and stenotic coronary vessels and remained unchanged in myocardium subtended by occluded vessels (Table 4).

**CABG Surgery**
Patients who underwent CABG during TEA received a median of 3 (range, 2 to 5) grafts. Median time to extubation after surgery was 0 minutes (range, 0 to 20 minutes); median intensive care unit stay was 1 day (range, 1 to 2 days); and median postoperative hospital stay was 6 days (range, 5 to 15 days). No ischemic events or cardiac deaths were recorded within 2 years after surgery. Within the observation period, 1 patient died in a drowning accident and 1 died of lung cancer.

**Discussion**
The present study demonstrates that TEA in patients with ischemic heart disease is associated with improved myocardial blood flow conditions. An increase in coronary vascular resistance by sympathetic stimulation was reverted to a decrease during TEA.

Epidural blockade of the upper thoracic nerve segments with local anesthetics results in an inhibition of the afferent sensory function and efferent sympathetic nervous innervation of the heart. Excellent pain relief may be achieved with this procedure in patients with angina pectoris refractory to medical treatment and after CABG.10,11,14 On the other hand, whether inhibition of the coronary sympathetic efferent innervation in ischemically jeopardized myocardium of patients with ischemic heart disease offers improved coronary function has been evaluated in only one previous study.19 Blomberg and coworkers19 found that TEA resulted in an increased epicardial coronary artery luminal diameter, yet they did not measure myocardial blood flow.

Whereas coronary innervation plays an important role during sympathetic nervous stimulation, the tone of this system appears to be of minor importance at rest.2,20 Accordingly, we found only minor changes in myocardial blood flow at rest during TEA.

The normal physiological response to sympathetic stimulation by the cold pressor test is a 30% to 45% increase in myocardial

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**TABLE 2. Hemodynamic Data for Cold Pressor Test Group**

<table>
<thead>
<tr>
<th></th>
<th>Without TEA</th>
<th>Cold Pressor Test</th>
<th>With TEA</th>
<th>Cold Pressor Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate, bpm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>56±7</td>
<td>73±16*</td>
<td>54±7</td>
<td>63±11†</td>
</tr>
<tr>
<td>Cold Pressor Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>118±10</td>
<td>149±20*</td>
<td>118±15</td>
<td>133±20±†</td>
</tr>
<tr>
<td><strong>Rate-pressure product</strong></td>
<td>6633±1026</td>
<td>10 838±2157*</td>
<td>6296±860</td>
<td>8523±2247‡</td>
</tr>
</tbody>
</table>

n=10. Values are mean±SD. *P<0.005 vs rest without TEA; †P<0.005 vs rest with TEA; ‡P<0.05 vs rest with TEA.

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**TABLE 3. Myocardial Blood Flow Response to Dipyridamole and the Cold Pressor Test**

<table>
<thead>
<tr>
<th></th>
<th>Without TEA</th>
<th>With TEA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dipyridamole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstenotic artery (0% to 49% stenosis)</td>
<td>39</td>
<td>0.69±0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.66±0.19</td>
</tr>
<tr>
<td>Stenotic artery (50% to 99% stenosis)</td>
<td>51</td>
<td>0.72±0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.73±0.24</td>
</tr>
<tr>
<td>Occluded collateral dependent artery</td>
<td>59</td>
<td>0.70±0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.58±0.23</td>
</tr>
<tr>
<td><strong>Cold pressor test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstenotic artery (0% to 49% stenosis)</td>
<td>17</td>
<td>0.73±0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75±0.17</td>
</tr>
<tr>
<td>Stenotic artery (50% to 99% stenosis)</td>
<td>78</td>
<td>0.81±0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.68±0.23</td>
</tr>
<tr>
<td>Occluded collateral dependent artery</td>
<td>50</td>
<td>0.63±0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.65±0.18</td>
</tr>
</tbody>
</table>

Values are mean±SD. Stimulated indicates during dipyridamole or cold pressor test.

*P<0.005 vs rest without TEA; †P<0.005 vs rest with TEA; ‡P<0.05 vs rest with TEA.
blood flow.\textsuperscript{2,16} Whereas the exact mechanism by which this mixed humoral-nervous sympathetic stimulation mediates coronary vasodilation is unknown, activation of both $\beta_{2}$-adrenergic receptors on coronary smooth muscle cells and $\alpha_{2}$-adrenergic receptors on endothelial cells with subsequent nitric oxide release has been suggested.\textsuperscript{21,22} In our patients with ischemic heart disease, myocardial blood flow during sympathetic stimulation remained unchanged in the face of a 65% increase in cardiac work estimated by the rate-pressure product, and an increase in the coronary vascular resistance was recorded. A similar highly abnormal coronary response to cold stimulation has previously been reported in patients with ischemic heart disease through the use of invasive methods.\textsuperscript{4,7} Increased coronary sensitivity to sympathetic stimulation and/or coronary endothelial dysfunction has been suggested to be responsible for this abnormality.\textsuperscript{5,7} In the present study, inhibition of cardiac sympathetic innervation by TEA resulted in a partial normalization of the coronary response to the cold pressor test. Depending on the vascular territory, myocardial blood flow increased from 17% to 100% during sympathetic stimulation and concomitant TEA (Figure 2). Previous observations have suggested that similar improvements in coronary function may be achieved by injecting mainly $\alpha$-adrenergic receptor inhibitors to the blood stream, emphasizing the role of the sympathetic nervous innervation in the modulation of coronary function.\textsuperscript{6} Nevertheless, the present study is the first to show that direct inhibition of cardiac nervous outflow in patients with ischemic heart disease is associated with a partial normalization of coronary function. Future studies of, for example, exercise tolerance during TEA should evaluate whether TEA increases the threshold of myocardial ischemia in patients with ischemic heart disease.

To evaluate the effect of TEA on near-maximal coronary vasodilatory function, we measured hyperemic blood flow during intravenous infusion of dipyridamole. Dipyridamole inhibits cellular reuptake and metabolism of endogenously released adenosine, producing submaximal coronary hyperemia uncoupled from regional metabolic regulatory mechanisms.\textsuperscript{23} Evaluation of the myocardial blood flow reserve with PET and dipyridamole infusion has proved valuable in determining the physiological impact of epicardial coronary structural abnormalities.\textsuperscript{16,24,25} Evaluating functional disturbances of coronary circulation with dipyridamole/adenosine was recently shown to be
difficult because vasodilation apparently can be mediated by several partly interdependent factors under such conditions, including smooth muscle cell relaxation, endothelial nitric oxide synthesis, and increased sympathetic tone.26–28 After TEA, only blood flow in myocardial regions subtended by collateral arteries displayed a slightly higher increase during dipyridamole infusion (Figure 2). Apparently, in coronary vessels with preserved anterograde blood flow, neural modification of dipyridamole-induced vasodilation is of minor importance. Some neural influence under these conditions was detected in myocardial subtended by collateral arteries; however, further studies are required to resolve the potential implications of this finding. As expected, the highest hyperemic blood flow was found in myocardium subtended by nonstenotic vessels, and as previously reported, hyperemic blood flow was significantly lower than in age-matched healthy subjects.29 This finding probably reflects the inability of coronary angiography to detect early phases of atherosclerosis and an overall impairment of vasomotor function in patients with ischemic heart disease.

Our findings may have important clinical implications. The observed improvement in coronary function during TEA in patients with ischemic heart disease may be advantageous during states of sympathetic activation for reducing the risk of developing myocardial ischemia. Accordingly, it was previously reported in patients undergoing CABG that TEA is associated with a significantly smaller release of troponin T 24 hours after intensive care admission compared with that in patients not receiving TEA.12 On the other hand, a recent meta-analysis including 1178 patients found that although TEA is associated with shorter time until tracheal intubation and decreased pulmonary complications and cardiac arrhythmias, no effect on mortality or rates of myocardial infarction could be found.30 However, most of the studies included in this meta-analysis were small (<50 treated patients), and because the pooled mortality rate of the study was low, the authors concluded that more larger-scale randomized controlled trials are required to fully assess the potential benefits of TEA for the reduction of myocardial infarction and mortality after CABG.

**Study Limitations**

Classification of myocardial segments as being subtended by nonstenotic, stenotic, or occluded coronary vessels was achieved by integrating coronary angiogram information and myocardial blood flow data.18 Consequently, some anatomical overlap between myocardial segments might occur, and our results should be interpreted accordingly.

The cold pressor test might not have evoked a stable hemodynamic response in all patients. However, systolic blood pressure, diastolic blood pressure, and heart rate were measured

### Table 4. Coronary Vascular Resistance

<table>
<thead>
<tr>
<th></th>
<th>Without TEA, mm Hg · ml⁻¹ · g⁻¹ · min⁻¹</th>
<th>With TEA, mm Hg · ml⁻¹ · g⁻¹ · min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Rest</td>
</tr>
<tr>
<td><strong>Dipyridamole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstenotic artery (0% to 49% stenosis)</td>
<td>39</td>
<td>133±73</td>
</tr>
<tr>
<td>Stenotic artery (50% to 99% stenosis)</td>
<td>51</td>
<td>122±75</td>
</tr>
<tr>
<td>Occluded collateral dependent artery</td>
<td>59</td>
<td>126±54</td>
</tr>
<tr>
<td><strong>Cold pressor test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonstenotic artery (0% to 49% stenosis)</td>
<td>17</td>
<td>108±29</td>
</tr>
<tr>
<td>Stenotic artery (50% to 99% stenosis)</td>
<td>78</td>
<td>101±29</td>
</tr>
<tr>
<td>Occluded collateral dependent artery</td>
<td>50</td>
<td>130±37</td>
</tr>
</tbody>
</table>

Values are mean±SD. Stimulated indicates during dipyridamole or cold pressor test.

*P<0.005 vs rest without TEA; †P<0.005 vs rest with TEA; ‡P<0.01 vs rest with TEA.
at 1-minute intervals and did not change significantly during our measurements. Thus, significant hemodynamic changes were unlikely to have occurred during the dynamic image acquisitions. The repeatability of myocardial blood measurements with PET during cold exposure is not known, yet serial measurements of coronary vasoreactivity during cold exposure with quantitative coronary angiography and with PET 20 days later produced similar results.31 Diabetic autonomic neuropathy associated with impaired vasodilator response cannot be ruled out as a con-
founder in our diabetic patients. On the other hand, no significant differences were noted with regard to myocardial blood flow responses in these and the remaining patients.

Although we demonstrated a beneficial effect of TEA on coronary blood flow in patients with ischemic heart disease, the design of our study did not allow evaluation of potential clinical correlates. Future studies should evaluate the extent to which improved coronary vasoreactivity during TEA may translate into symptom-
atic improvement in patients with ischemic heart disease.

Conclusions

In the present study, we have demonstrated that TEA partly normalizes the myocardial blood flow response to sympathetic stimulation in patients with multivessel ischemic heart disease.

Acknowledgments

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