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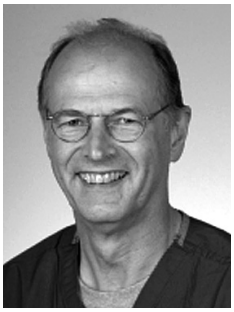
In dedication to our scientific mentor and friend Prof. Dr. Hans Sonntag

High thoracic epidural anaesthesia in patients undergoing CABG reduces sympathetic effects on myocardial blood flow and myocardial oxygen uptake and its effect on myocardial ischemia



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Implications Statement

In a prospective randomized study on patients undergoing coronary artery bypass grafting high thoracic epidural anaesthesia (HTEA) significantly reduced myocardial blood flow without provoking ischemia. A clinically relevant reduction of oxygen consumption due to HTEA-related attenuation of sympathetic response supports the hypothesis that HTEA provides cardio-protective effects.

Summary

Background. High thoracic epidural anaesthesia (HTEA) has been known to reduce sympathetic response in patients undergoing coronary artery bypass grafting (CABG). The aim of this study was to prove the effects of HTEA combined with a general anaesthetic on myocardial oxygen supply and demand. ***Methods.*** The study was carried out prospectively in 20 caucasian males randomized to receive either general anaesthesia with HTEA (Group I) or general anaesthesia without HTEA (Group II). In Group I a thoracic epidural catheter (T 2-4) was placed the day prior to surgery with fluoroscopic guidance. The day of surgery data collection began prior to induction, after induction, after loading the epidural catheter with Bupivacaine 0.5% (in group I, after corresponding time delay in group II), and during sternotomy. Primary endpoints included myocardial blood flow (modified Kety-Schmidt method), myocardial oxygen balance, metabolic markers of ischemia measured in the coronary sinus and hemodynamic variables. Nonparametric statistical description and analysis was applied (Mann-Whitney-test). ***Results.*** The results showed greater diminution of sympathoadrenergic impact on hemodynamic variables, leading to reduction of factors of myocardial oxygen requirements and resulting in reduced left ventricular $dPdt_{MAX}$ and significantly less myocardial oxygen requirements. Myocardial blood flow was significantly reduced without effecting markers of ischemia. ***Conclusion.*** A clinically relevant reduction of oxygen consumption due to HTEA-related attenuation of sympathetic response was evident. HTEA appears to be cardio-protective in patients undergoing CABG. *Anestezjologia i Ratownictwo 2011; 5: 150-160.*

Keywords: endotracheal intubation, endotracheal tube cuff, cuff pressure, intubation complications

Introduction

For many years much effort has been made to improve the perioperative outcome of patients with coronary artery disease [1-3]. Besides optimal medical management and sophisticated surgical approaches modern anaesthetic techniques have improved outcomes by providing more hemodynamic stability during anaesthesia and surgical stress resulting in better myocardial oxygen balance and therefore diminishing myocardial ischemic events. However, patients undergoing CABG surgery still face a considerable risk of morbidity resulting from perioperative ischemia, arrhythmia and thrombotic events. Many of the current anaesthesia techniques have not always proven to protect the myocardium from increased sympathetic nervous stimulation during induction of anaesthesia and surgical stress leading to increased heart rate, myocardial contractility and loading conditions of the ventricle – the major determinants of myocardial oxygen consumption [4].

In animal models as well as in human studies the use of high thoracic epidural anaesthesia (HTEA) has been shown to provide cardiac protection during CABG by decreasing sympathetic nervous system output [5]. HTEA decreases ST-segment changes and dysrhythmias and increases the diameter of excentricly stenotic coronary vessels improving blood flow. It has also been suggested that part of the cardio protective effect involves reduction of workload of the heart and consequently a reduced myocardial oxygen demand [6].

The study was designed to quantify the effect of HTEA on myocardial oxygen consumption ($MV0_2$) and coronary blood flow (MBF) in relation to hemodynamic factors which determine $MV0_2$ and MBF in patients undergoing CABG. In addition to coronary blood flow, lactate and hypoxanthine were measured in the arterial and coronary sinus blood as indices of anaerobic myocardial metabolism.

Methods

The study and data analysis were performed in collaboration with the cardiac research group, Department of Anaesthesiology, University of Goettingen, Germany and the Department of Anaesthesia and Perioperative Medicine, Medical University Charleston, SC. The study design was approved by the Human Review Committee of the University of Goettingen (N* 15 II 94).

20 patients (ASA physical status II-III) scheduled for coronary artery bypass surgery were enrolled in the study. Each patient gave written informed consent the day before surgery. All of them were randomly assigned (envelope method) in either a group with thoracic epidural anaesthesia (group I) or in a group without (group II). Exclusion criteria included patients aged over 70 years, history of congestive heart failure, ejection fraction less than 40%, valvular heart disease, liver disease, metabolic disorders, platelet count less than 120.000, partial thromboplastin time over 40 sec and thrombin time greater than 22 sec, baseline neurologic deficits, or infections at the site of epidural insertion. All cardiac medications (beta-blockers, nitrate, calcium channel blockers, etc) - except of aspirin, which was stopped 7 days before surgery - were continued through the morning of surgery.

In group I a thoracic epidural catheter (T 2-4) (19G, Vygon, Aachen, Germany) was placed the day prior to surgery using loss of resistance to saline technique with an 18-gauge Touhy needle (Vygon, Aachen, Germany), the catheter was inserted 3 cm into the epidural space then tunneled subcutaneously 6-8 cm. Placement was confirmed by fluoroscopy.

All patients received flunitrazepam (2 mg orally) as premedication one hour before they were transferred to the induction room. There ECG leads were attached to the patient and an iv. line instituted. Before placing all catheters necessary for anaesthesia and measurements 5000 units of heparin were administered intravenously.

Under local anaesthesia using Seldinger technique the following catheters were placed:

- A 6F Goodale-Lubin catheter via the right internal jugular vein into the coronary sinus, for myocardial blood flow measurements and withdrawal of blood samples for biochemical analysis.
- An 18-gauge catheter connected to a 6F Goodale-Lubin catheter with the identical dead space of the coronary sinus catheter into one radial artery for measuring hemodynamics and for blood samples.
- A Swan-Ganz thermodilution catheter (Edwards N* 93 A 131-7F, Irvine CA, USA) via a second 8,5 French port (Arrow REF CI-09800, Reading PA, USA) in the right internal jugular vein into the pulmonary artery for cardiac output, pulmonary artery pressure and wedge pressure measurement.
- A 3F Millar-Tip catheter through the femoral artery into the left ventricle to obtain left ventricular end-diastolic pressure (LVEDP) and the

first derivative of left ventricular pressure increase ($dPdt_{MAX}$).

Placement of all catheters was confirmed by fluoroscopy.

Finally, a Foley catheter with an incorporated temperature probe was placed. ECG, body temperature and hemodynamic parameters were monitored continuously and recorded on a 10 channel strip chart recorder (Siemens AG, Muenchen, Germany). A Life Scan (Braun, Melsungen, Germany) cerebral function monitor for measurements of depth of sedation was attached. Derived variables such as coronary-, pulmonary- and peripheral vascular-resistance, cardiac-output and stroke volume index were calculated according to standard formulas. Hypoxanthine release, a lactate uptake and release were measured in the arterial and coronary venous blood. After placement of all catheters patient had time to rest for 30 min before starting the baseline measurements. The first measurement (M I) was performed in the awake patient. Then general anaesthesia was induced. 20 min after induction the 2nd measurement was taken (M II). Next the epidural catheter was loaded with Bupivacaine (Carbostesin® 0.5%, AstraZeneca, Wedel, Germany). The 3rd measurement was made 30 min after dosing the thoracic epidural catheter (M III). The 4th measurement was taken during sternotomy and sternal spread (M IV), which was about 50 min later.

Anesthesia was induced in both groups after breathing 100% oxygen via a face mask for 5 min. Sufentanil 2 $\mu g \cdot kg^{-1}$as a bolus dose, followed by an infusion of sufentanil 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (Sufenta® Janssen-Cilag, Neuss, Germany). Hypnosis was maintained with midazolam 1.5-3mg bolus (Dormicum® Roche, Grenzach, Germany) according to Life Scan readings. Tracheal intubation was facilitated by 0.1 $mg \cdot kg^{-1}$ pancuronium and controlled ventilation commenced with 40% oxygen in air using a Cicero-Respirator (Draeger, Lűbeck, Germany).

The epidural was dosed using Bupivacaine 0.5% with reference to body height of patients. After a bolus of 200 µg/cm body height, a continuous infusion of 200 µg/cm body height per hour with a 0.25% Bupivacaine solution was given via a syringe pump.

Myocardial blood flow (MBF) was measured after inhalation of a standard concentration of argon in oxygen (70/30%) with simultaneous and continuous blood sampling (via a modified syringe pump, Braun Melsungen, Germany) from the radial artery and the coronary sinus [7]. The method is based on the Fick-principle (1872) and on the Kety-Schmidt method and is described elsewhere [8].

Immediately before and after each measurement of myocardial blood flow and hemodynamics arterial and coronary venous blood samples were taken for blood gases and acid base status, electrolytes, plasma levels of catecholamines (HPLC-EC, Bioanalytica systems), lactate (enzymatically), plasma levels of hypoxanthine (Merck-Hitachi 655 A-40 Auto sampler). Oxygen content in arterial and coronary sinus blood was directly measured with a Lex-O_2-Con as well calculated from hemoglobin concentration, O_2-Saturation and O_2-tension to verify the measured value. Lactate release and uptake were calculated by multiplication of the arterial-coronary venous lactate difference by MBF.

Statistics

Patient characteristics were described as median with maximal and minimal values. Differences between Medians were calculated using the Mann-Whitney test. Statistical significance was accepted at $P < 0.05$.

Results

Between the two groups no significant differences in age, weight, body surface area, and ASA physical status were shown. There was a difference with respect to angiographic preconditions, two patients in group I and three in group II had evidence of left ventricular hypokinesis.

Table 1. Demographic Data

		group I (with HTEA)	group II (without HTEA)
number	[n]	10	10
age	[years]	59.8±6.3	62.1±5.9
height	[cm]	171.2±5.6	172.7±4.7
weight	[kg]	80.2±14.3	82.7±9.2
surface area	[m^2]	1.92±0.17	1.96±0.11
EF	[%]	69.3±10.6	64.2±6.1

Demographic and hemodynamic data are presented in Tables 1, 2 and 3. Heart rate, systolic and diastolic pressure decreased after induction at M II and further at M III in both groups, but more pronounced in group

I. The intra-group differences increased during sternotomy and sternal spread but to a lesser degree in group I. The mean arterial pressure (MAP) decreased in both groups after induction of anaesthesia. This pressure drop was significantly lower in the group I. During surgical stimulus there was an increase of MAP, which was significantly lower group I than in group II.

Left ventricular end-diastolic pressure (LVEDP) and dP/dt_{MAX} were significantly lower in group I. The $dPdt_{MAX}$, dropped in both groups after induction of anaesthesia. This decrement became significant after loading the epidural catheter in group I. In this group the values remained significantly lower throughout the operative course, including during sternotomy.

The myocardial blood flow decreased significantly after induction of anaesthesia in both groups and particularly after loading the epidural catheter in group I. Even with an increase in blood pressure, MBF remained constant in this group.

The myocardial oxygen consumption decreased also after induction in both groups. In group I the values remained diminished, staying significantly lower compared to group II during sternotomy. Myocardial oxygen consumption increased in group II significantly during sternotomy, whereas values remained almost constant in group I. So induction of anaesthesia was not only followed by a decrease in myocardial oxygen consumption and myocardial

Table 2. Hemodynamic Data

		without	with	without	with	without	with	without	with
		I		II		III		IV	
HR	[1·min⁻¹]	64^{86}_{43}	73^{113}_{57}	61^{92}_{42}	73^{107}_{56}	$60.0*^{85}_{44}$	62^{77}_{53}	$80.0*^{96}_{50}$	65^{94}_{54}
Psyst	[mmHg]	166^{197}_{137}	176^{198}_{120}	126^{162}_{99}	124^{151}_{91}	$115.0*^{141}_{101}$	96^{117}_{70}	$138.0*^{156}_{117}$	121^{137}_{93}
Pdist	[mmHg]	82^{94}_{63}	76^{95}_{56}	65^{95}_{51}	66^{78}_{42}	$61.5*^{82}_{49}$	50^{58}_{36}	$77.0*^{100}_{62}$	66^{80}_{50}
MAP	[mmHg]	114^{126}_{88}	112^{127}_{77}	85^{117}_{68}	83^{102}_{58}	$80.0*^{103}_{66}$	63^{77}_{47}	$94.7*^{119}_{82}$	84^{99}_{64}
MPAP	[mmHg]	$15.5^{24.3}_{10.3}$	$19.7^{25.3}_{10.0}$	$15.2^{25.3}_{10.0}$	$16.5^{20.3}_{12.3}$	$15.7^{24.7}_{10.7}$	$13.9^{20.0}_{12.0}$	$18.0^{23.0}_{10.3}$	$19.0^{23.0}_{13.7}$
CVP	[mmHg]	$5.5^{11.0}_{1.0}$	$5.5^{14.0}_{0.0}$	$6.0^{11.0}_{3.0}$	$6.5^{16.0}_{2.0}$	$7.0^{11.0}_{2.0}$	$6.0^{10.0}_{3.0}$	$11.0^{16.0}_{3.0}$	$9.5^{18.0}_{6.0}$
SVR	[dyn·sec·cm⁻⁵]	$1614*^{2199}_{1417}$	1444^{1644}_{1181}	$1510*^{2430}_{1167}$	1271^{1494}_{888}	$1465*^{2195}_{1083}$	1095^{1491}_{627}	1450^{1860}_{1209}	1330^{1655}_{1024}
LVEDP	[mmHg]	$11.0^{16.0}_{6.0}$	$9.8^{14.0}_{7.3}$	$10.5^{13.0}_{8.0}$	$9.9^{12.0}_{8.0}$	$11.0^{14.0}_{9.0}$	$12.0^{13.5}_{6.9}$	$13.0^{16.0}_{6.0}$	$12.3^{14.6}_{10.8}$
dp/dtmax	[mmHg/sec]	875^{1125}_{700}	963^{1250}_{800}	800^{900}_{475}	700^{900}_{600}	$675*^{775}_{500}$	525^{650}_{450}	$775*^{925}_{575}$	638^{800}_{475}
CI	[L/min·m⁻²]	$2.7*^{2.90}_{2.00}$	$2.99^{3.61}_{2.40}$	$2.07*^{2.71}_{1.66}$	$2.53^{3.61}_{2.15}$	$2.10^{2.74}_{1.46}$	$2.12^{3.15}_{1.68}$	$2.44^{2.98}_{1.84}$	$2.27^{2.97}_{1.53}$
SVI	[ml·m⁻²]	$39.3^{52.5}_{31.1}$	$38.4^{53.2}_{32.0}$	$32.5^{39.5}_{22.5}$	$34.6^{48.1}_{29.5}$	$33.8^{42.5}_{22.9}$	$35.1^{50.8}_{25.0}$	$33.0^{40.6}_{20.6}$	$34.9^{46.4}_{24.2}$

* = Statistically significant at time of measurement between groups
$p < 0.05$

HR Heart Rate
Psyst Systolic Blood Pressure
Pdist Diastolic Blood Pressure
MAP Mean Arterial Pressure
MPAP Mean Pulmonary Artery Pressure
CVP Central Venous Pressure
SVR Systemic Vascular Resistance
LVEDP Left Ventricular End Diastolic Pressure
dp/dtmax first derivative of left ventricular pressure over time
CI Cardiac index
SVI Stroke volume index

Data are presented as median values with maximal (superscript) and minimal (subscript) values of each group

Table 3. Data on myocardial perfusion, oxygen balance, and metabolism

		without		with		without		with		without		with		without		with	
		I				II				III				IV			
MBF	[ml/min·100g]	96	127 67	98	107 68	77	100 65	78	96 59	85.5*	107 49	57	86 46	97*	176 78	65	90 46
MVO_2	[ml/min·100g]	11.8	15.9 6.9	12.9	17.0 7.8	8.3	11.4 5.4	9.4	13.4 5.5	9.0	11.0 5.2	5.8	10.8 3.9	10.6*	16.7 7.0	6.9	11.1 4.6
CVR	[mmHg/ ml·min·100g]	1.07	1.53 0.75	1.08	1.44 0.87	0.96	1.64 0.76	0.93	1.24 0.73	0.86	1.43 0.68	0.97	1.24 0.71	0.84*	1.13 0.52	1.13	1.50 0.68
Lact avD	[µMol/ml]	0.08	0.33 -0.11	0.09	0.34 -0.58	0.03	0.34 -0.01	0.06	0.15 -0.34	0.00	0.29 -0.11	0.05	0.13 -0.24	0.09	0.64 -0.21	0.05	0.16 -0.27
Hpx avD	[µMol/ml]	0.07	0.52 -0.06	0.04	0.25 -1.41	0.10	0.72 -0.64	0.06	0.41 -1.44	0.05	0.41 -0.27	0.23	0.53 -1.00	0.16	0.39 -0.09	0.17	0.45 -0.13
Adren.	[picog/ml]	203	371 96	238	997 159	196	463 64	210	646 131	158	328 43	183	434 53	253	461 68	203	557 43
$O_2S_{cor.ven.}$	[%]	31	37 27	30	39 26	37	57 28	36	44 30	37	46 31	38	48 35	37	44 30	42	45 35
$O_2S_{art.}$	[mmHg]	98	99 97	98	99 94	99	99 98	99	99 95	99	99 98	99	99 98	99	99 98	99	99 98
P_aCO_2	[mmHg]	40	53 33	41	51 35	42	47 37	42	46 37	44	47 37	42	46 36	43	61 39	39	46 34
pH		7.428	7.468 7.397	7.426	7.473 7.367	7.401	7.485 7.374	7.408	7.452 7.372	7.399	7.475 7.349	7.411	7.467 7.345	7.401	7.486 7.313	7.446	7.488 7.378

* = Statistically significant at time of measurement between groups

$p < 0.05$

MBF Myocardial Blood Flow

MVO_2 Myocardial Oxygen Consumption

CVR Coronary Vascular Resistance

Lact avD Arterial Coronary Lactate Concentration Difference

Hpx avD Arterial Coronary Hypoxanthine Concentration Difference

Adren. Adrenaline

$O_2S_{cor.ven.}$ Coronary Venous Oxygen Saturation

$O_2S_{art.}$ Arterial Oxygen Saturation

P_aCO_2 Arterial Carbon Dioxide Partial Pressure

pH_{art} Arterial pH

Data are presented as median values with maximal (superscript) and minimal (subscript) values of each group

blood flow, but also by a reduction of coronary vascular resistance (CVR). Dosing the epidural was followed by a further significant reduction of MVO_2 and MBF, as it could be seen at measurement points III and IV (Table 3).

Cardiac index was reduced after induction of anaesthesia in both groups throughout all postinduction measurements. Patients of group II showed a higher increase during sternotomy than patients of group I. The systemic vascular resistance index was significantly lower in group I prior to induction of anaesthesia; also the trend of the values was lower. Correspondingly the cardiac stroke volume index was lower in group I prior to induction. During the course the SVI decreased in both groups, but less in group I.

Adrenalin plasma levels demonstrated large individual variation. There were higher levels in group I at base line than in group II. After induction of anaesthesia at measurement points M II and MIII the epinephrine levels were lower in both groups compared to the baseline values. At measurement point IV the epinephrine level increased during sternotomy and sternal spread in group II, whereas in group I a further decrease in plasma levels of epinephrine occurred.

Though no statistical inference can be made on a single patient, the authors feel it is important to highlight several illustrative patients. One patient in Group II (pat. No 3) showed a negative lactate balance at point IV which was not correlated to hypoxanthine release. This was coincident with a decrease in mean arterial pressure from 112 to 82 mmHg and a marked increase in heart rate from 43 min^{-1} at base line to 89 min^{-1}during sternotomy. Another patient (pat. No 16) had a hypoxanthine release but not a negative

lactate balance which was without relation to hemodynamic changes. A further patient (No 14 in group I) demonstrated at measurement point IV a lactate and a hypoxantine release into the coronary sinus indicating an ischemic event. This patient had a high mean arterial pressure of 115 mmHg at baseline. After loading the epidural catheter, MAP dropped to 47 mmHg and at sternotomy it increased to 97 mmHg. This patient also was tachycardic throughout the study. Patient No 15 of group I experienced a hypoxanthine release but no negative lactate balance was shown with no relation to hemodynamic changes.

Patients who had a negative lactate balance and/or hypoxantine release at sternotomy did not show any ST-segment changes in lead II or V. During the entire study period pH, body temperature, blood gas tension, arterial and coronary O_2 saturation as well as the $PaCO_2$ stayed within the normal ranges.

The figures 1 and 2 are showing all single points of lactate extraction together with hypoxanthine release and myocardial oxygen consumption measurements for both groups with MVO_2 on the ordinates and LE on the abscissas. Solid points indicate the coincidence of negative myocardial lactate extraction and hypoxanthine release. Both figures demonstrate a wide scatter of data without linear correlation between LE

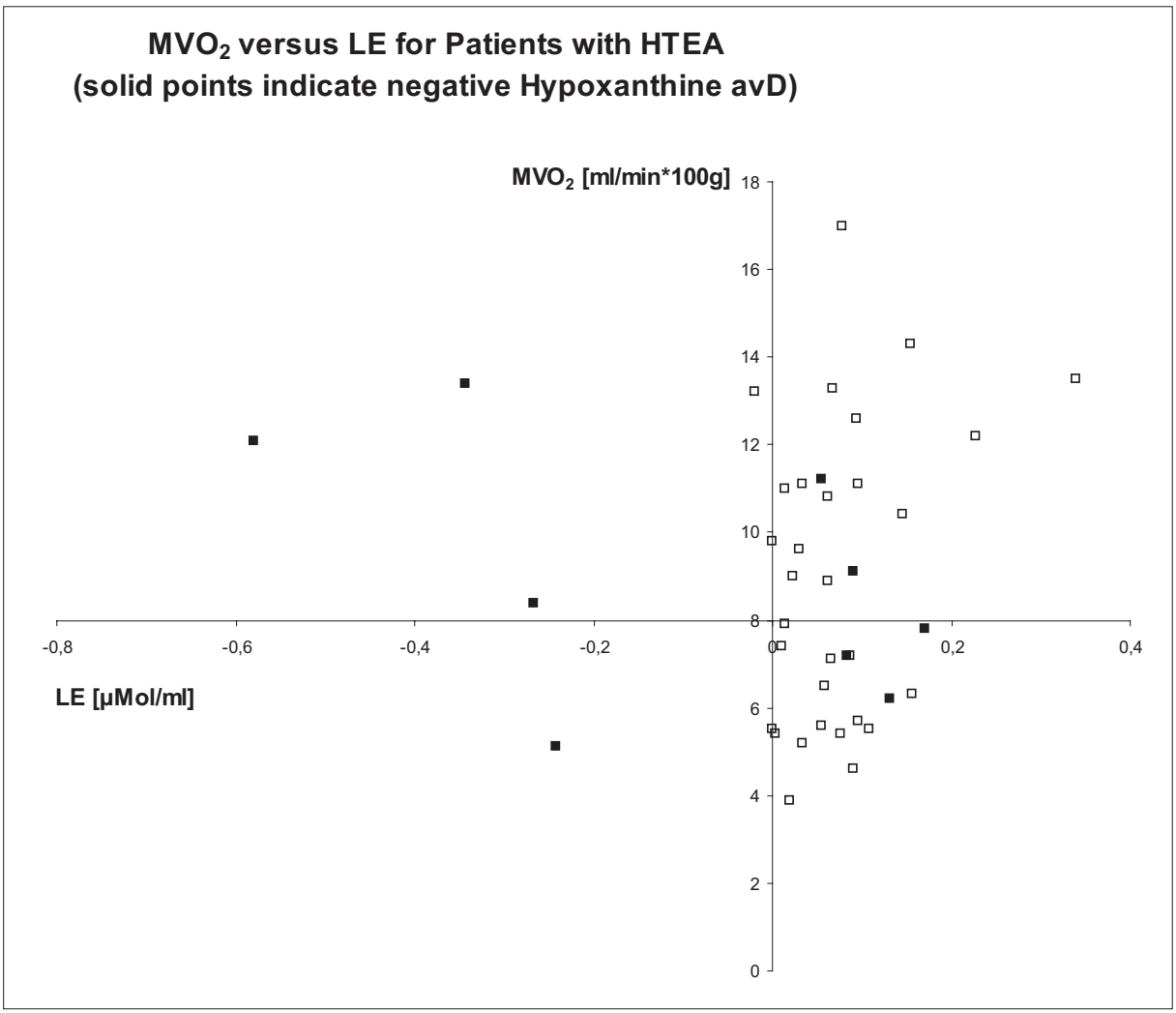

Figure 1. Showing the lactate extraction (LE) and hypoxanthine release of patients of group I at measurement points I - IV in relation to myocardial oxygen consumption (MVO_2)

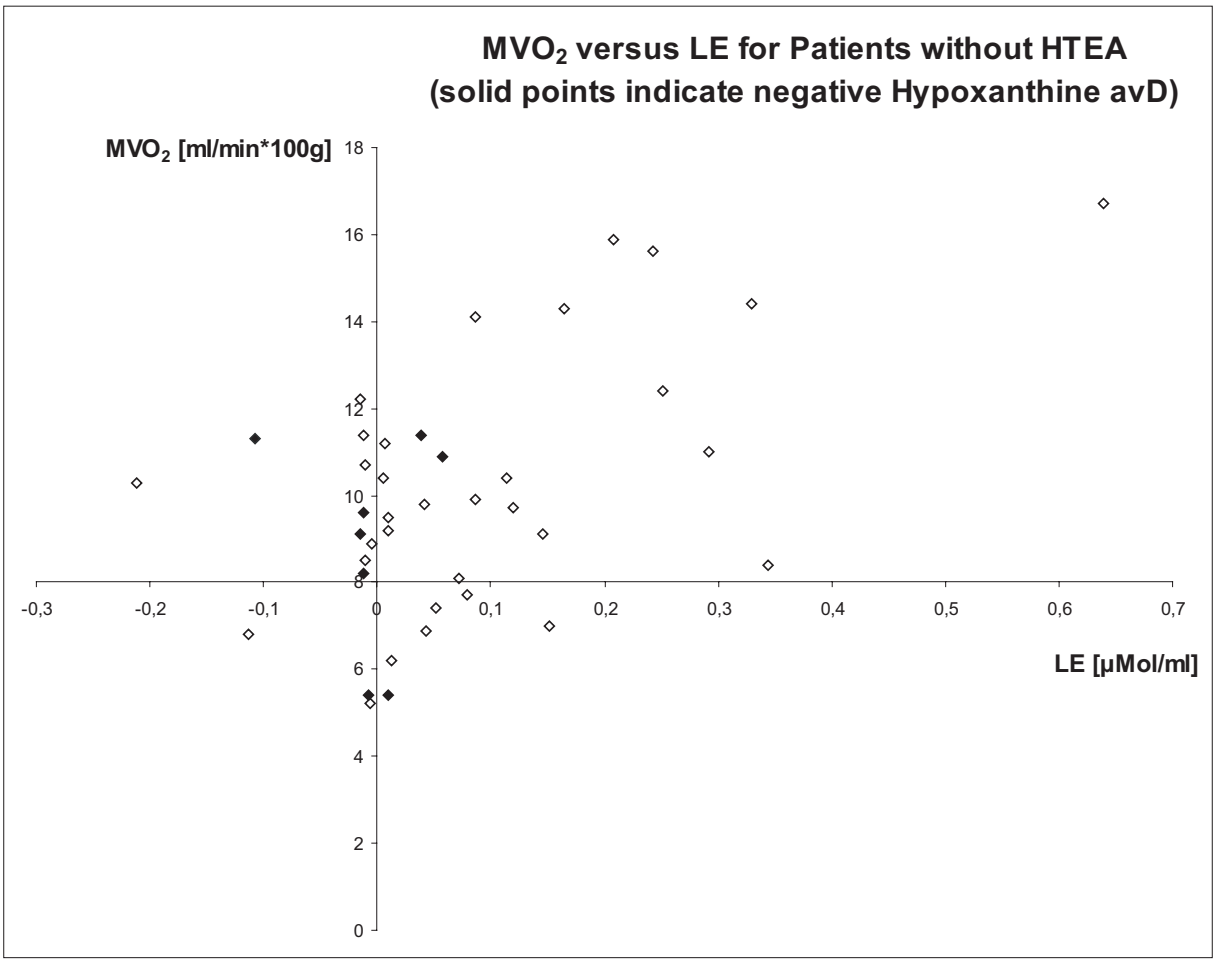

Figure 2. Showing the lactate extraction (LE) and hypoxanthine release of patients in group II at measurement points I - IV in relation to myocardial oxygen consumption (MVO_2)

and MVO_2. For group I the single points of measurement are distributed more in the lower range of MVO_2 than in group II, indicating that this group had lower overall myocardial oxygen consumption. But in spite of the reduction of the myocardial blood flow, the figures show that this did not cause a higher incidence of lactate and/or hypoxanthine release indicative for occurrence of ischemia.

Discussion

This study aimed to prove whether HTEA combined with a general anaesthetic could contribute to better myocardial oxygen supply and lower demand**.** The results showed the reduction of factors of myocardial oxygen requirements, i.e. reduced left ventricular $dPdt_{MAX}$ and greater diminution of sympathoadrenergic impact on hemodynamic variables. This allowed the myocardial blood flow to be significantly reduced without effecting markers of ischemia-this should be the first sentence of the discussion.

Some authors have argued that methods of anaesthesia do not influence long term outcome [9]. Nevertheless attempts continue to find the best choice of anaesthetics and ways to deliver cardio-protective anaesthesia. In this context the use of high thoracic epidural anaesthesia in cardiac anaesthesia offers some beneficial effects [5,6,10], although it is not free from adverse effects and risks.

Kock et al [6] examined patients with coronary artery disease and severe stable angina, being exposed to exercise induced stress under metoprolol and

high thoracic epidural anaesthesia. The induction of HTEA reduced major determinants of myocardial oxygen demand while improving global and regional left ventricular wall motion detected with a gamma camera and reduced signs of myocardial ischemia. They speculated that not only pain control was achieved, but also alpha-adrenoceptor-mediated vasoconstriction of stenotic epicardial arteries could be blunted by HTEA.

Kirnoe et al [10] performed a study on 20 patients undergoing CABG and tested HTEA as an adjunct to general anaesthesia against a control group without HTEA. In conclusion they found that HTEA attenuates intraoperative sympathetic activity preventing increased myocardial oxygen demand under stable hemodynamic conditions.

The specific requirements of patients with poor left ventricular function have been focused on by Kilickan et al [5]. They concluded from their investigations that HTEA appeared to be advantageous in terms of improved cardiac index, reduced arrhythmias, and decreased inotropic requirements.

In order to learn even more about possible ways to protect the myocardium by anaesthetic methods, it is mandatory to exploit encouraging results from animal experiments and previous clinical studies and derive designs of studies on patients with coronary artery disease. Although the advantage of models of myocardial ischemia are much more reliable in terms of showing effects under controlled and reproducible ischemia, the findings need to be transferred to medical practice, so clinical studies allow direct implications on routinely applied methods that seem to be beneficial.

This study aimed to quantify the effect of HTEA on coronary blood flow and myocardial oxygen consumption, at the same time uncover the influence on myocardial metabolism using lactate and hypoxantine levels. Both substances are degradation products of ATP produced under anaerobic conditions and as such sensitive markers of myocardial ischemia [11,12]. Patients who had a negative lactate balance and/or hypoxantine release at sternotomy did not show any ST-segment changes in lead II or V. This might be due to the "different" position of electrodes after sternotomy and sternal spread.

There are methodological challenges to proving acute ischemic events of the myocardium. Backstrom et al [12] investigated the cardiac outflow of amino acids and purines during myocardial ischemia and reperfusion using microdialysis catheters in the great cardiac vein in animal experiments. They described reproducible and significant increases of hypoxanthine concentration in the myocardial venous blood unambiguously correlated with length of ischemia, with exponential decrease during reperfusion. Harmsen et al [13] demonstrated that hypoxanthine measurements of myocardial arterial-venous differences in patients undergoing atrial pacing stress tests have been useful in determining myocardial ischemia and detecting ischemic heart disease.

Although myocardial lactate excretion as well as coronary venous hypoxanthine are proven markers of ischemia, there is an apparent lack of coincidence. An explanation might be the consideration that the arterio-coronary venous difference of lactate always represents a mixture of normally and insufficiently perfused areas. In some situations the worst ischemic regions might produce lactate whereas other regions maintain their physiologic uptake of lactate, so both phenomena end up with a normal appearance of the overall arterial-coronary venous lactate concentration difference. However, taking all this into account, at least the combination of hypoxanthine release together with negative arterial-coronary-venous lactate balance represents myocardial ischemia.

In the patients of this study no significant differences of the course of arterio-coronary-venous Lactate and Hypoxanthine levels between groups could be found. Nevertheless there are several points of measurements with evidence of myocardial ischemia based on coincidence of hypoxanthine release and negative lactate balances. The most impressive course was measured in patient 14 of group I with HTEA, who showed the most negative lactate levels and hypoxanthine release of both groups. A considerable decrement of intensity of ischemia took place in this patient after loading the epidural catheter and applying transient sympathectomy. This effect was consistent for all following points of measurement in this patient. Although this is only one patient, the observed phenomenon could be interpreted as a case demonstrating the established improvement of the oxygen balance of the myocardium under distress and resulting ischemia. With the transient sympathectomy from HTEA this particular ischemic myocardium might have had real benefit.

However, as it is shown in figure 1 and 2, there was neither a correlation between myocardial oxygen uptake and negative lactate nor negative hypoxanthine differences with relation to MVO_2. The graphs show

that HTEA reduced the myocardial oxygen consumption without shifting the lactate extraction or hypoxanthine release together with negative lactate extraction into a range indicative of myocardial ischemia, as it would be expected from considerations of reduced myocardial blood flow.

Our study was focused on whether HTEA was able to blunt the stress response to sternotomy and sternal spread, as several studies have shown that even with high doses of opioids ("industrial dosing", e.g. fentanyl 100 μg/kg) sternotomy results in increased blood pressure and/or heart rate (e.g. sympathetic stress response) [19], it is quite unlikely to assume this reaction might be due to unrelieved pain. Since stress produces increases in plasma levels of adrenalin, which in turn becomes the onset of a variety of mechanisms influencing myocardial oxygen balance during anaesthesia and surgery, epinephrine levels were measured at times where increases in catecholamines were expected. As it has been demonstrated, HTEA could diminish epinephrine release secondary to a possible residual pain perception or due to a blockade of efferent sympathetic stimulation.

The changes of myocardial metabolic and global hemodynamic parameters reflect changes of the sympathoadrenergic tone induced by general anaesthesia alone or by general anaesthesia in combination with HTEA. From this point of view, the shift of hemodynamics and the reduction of inotropism together with increasing left ventricular end diastolic pressures might be the result of a functionally reversible, transient sympathectomy due to HTEA causing reduced myocardial work load.

A reduced level of sympathoadrenergic activity with corresponding reduction in metabolic requirements should cause a decrease in myocardial effort and thus reduce the demand of oxygen. Under this assumption, the parameters of myocardial blood flow and oxygen consumption might be expected to also be lowered.

Although all patients of both groups were anaesthetized with attention to maintain hemodynamic and laboratory parameters within physiological ranges yielding neither negative values of Base Excess in the coronary venous blood nor other relevant disturbances, patients with HTEA clearly showed reduced myocardial oxygen requirements. This might be interpreted as a result of a better sympathicolysis by HTEA and confirming the hypothesis that combined general anaesthesia with HTEA provides improved balance between reduced metabolic requirements of the myocardium and oxygen supply.

Studies on myocardial ischemia in humans suffer a variety of methodological drawbacks. Since ischemia requires instantaneous treatment, its occurrence would always be limited and transient. Also ischemia in human myocardium reflects the pathophysiologic outcome of complex mechanisms due to circulating catecholamines, hemodynamics, intrinsic actions of circulating metabolites and mediators, platelet function, and pathoanatomical constellations with atherosclerotic damages of intravascular and endothelial surfaces. This complex pathophysiology is reflected by the fact, that meta analysis of HTEA in cardiac surgery is not able to show a significant benefit on mortality and myocardial infarction of adding regional sympathoadrenergic blockade (HTEA) to general anesthesia [17]. Moreover, as long as hemodynamic conditions are stable, myocardial ischemia is in any case a phenomenon of a given region of the myocardium, and related to a highly individual coronary anatomy and pathology.

In this study the attempt was made to exclude other effects on cardiovascular responses, myocardial metabolics and hemodynamical impacts than those due to the applied epidural analgesia and the general anesthesia. General anesthesia was performed according to the standard at our institution (e.g. total intravenous anesthesia with sufentanil 2-3 μg/kg induction dose and 1μg/kg/h maintenance, supplemented with midazolam bolus (1.5-3 mg). This regime has been confirmed by others to be appropriate yielding hemodynamically safe and stable conditions [18].

With the tremendous scatter of most parameters in relation to the number of patients enrolled in our study, nonparametric statistical analysis did not reveal many significant differences. Nevertheless, the trends of our data show that the group with HTEA started with higher plasma levels of epinephrine but had a more profound decrease and stability during the course and during sternotomy compared to group II without HTEA. Our study is underpowered to make prognostic assertions regarding outcome for patients with CABG having HTEA or not, but this was no aim of our investigation. However, our results indicate, that HTEA might be an important contribution to myocardial protection with limitation of the adrenergic response, decreased myocardial work and improved myocardial oxygen balance.

To our knowledge there are no prospective randomized studies on humans with coronary artery disease undergoing cardiac surgery employing direct measurements of left ventricular pressures and characteristics of inotropic status together with myocardial blood flow based on determination of volumes over time, and humoral direct markers of myocardial ischemia done with respect to high thoracic epidural anesthesia.

Recent publications of effects of thoracic epidural catheters aimed to provide data about primary endpoints like 30-days-free-from-myocardial-infarction, pulmonary complications, renal failure, and stroke as well as these parameters after 1 year [14]. The authors could not prove beneficial effects due to HTEA, but – moreover – they could not describe from their setting, why the provided sympathicolysis from HTEA did not contribute to any benefit, even though they enrolled very large numbers of patients. So the question remains, what in detail was failing to positively influence outcome with a clinically well established and uncontradicted anesthesiologic technique like analgesia and sympathicolysis from HTEA during surgery? Although particularly this would be clinically most interesting, it remains unanswered, because in contrast to our study those investigations could not provide detailed information about above mentioned physiological phenomena related to HTEA. Although outcome studies are of course of extreme importance for clinical decision making, it thus may also be highly important and useful for the assessment of conditions in individual patients and/or situations to know details about possibilities and achievable beneficial effects on myocardial oxygen balance with HTEA.

In this respect the limited number of enrolled patients is due to the extremely high technical demands and sophisticated catheterizations. On the other hand there is the advantage of our study given by the high resolution of illustrated effects on myocardial oxygen balance and its most important affecting factors. It may also be mentioned that other studies aiming at explorations of more detailed pathophysiological phenomena requiring extensive catheterizations have enrolled similar numbers of patients [10].

Like most other authors, we did not find any sequelae or neurologic complications in our patients although there are considerable risks of spinal hematoma formation from HTEA. Salvi et al [15] confirmed from their study with 476 patients that there were no neurologic complications and also Scott et al [16] reported from their study with 179 patients that no adverse neurologic issues occurred. In spite of these reports anaesthesiologic concerns have always been focused on epidural bleeding and consecutive sequelae. Particularly as a full anticoagulation has to be provided for extracorporal circulation, the puncture and insertion of the epidural catheter the night prior to surgery would be the safest approach and revealed to be safe in our patients.

In conclusion this study shows a clinically relevant reduction of oxygen consumption due to HTEA-related attenuation of sympathetic response thereby providing cardio-protective effects in patients undergoing CABG.

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Piśmiennictwo

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