Effects of thoracic epidural analgesia on exercise-induced myocardial ischaemia in refractory angina pectoris

Adrian Gonon, Arina Richter, Ingemar Cederholm, Jehangir Khan, Jacek Novak, Micha Milovanovic and Birgitta Janerot-Sjoberg

The self-archived postprint version of this journal article is available at Linköping University Institutional Repository (DiVA):
http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-155522

N.B.: When citing this work, cite the original publication.
https://doi.org/10.1111/aas.13291

Original publication available at:
https://doi.org/10.1111/aas.13291

Copyright: Wiley
http://eu.wiley.com/WileyCDA/
Effects of thoracic epidural analgesia on stress-induced myocardial ischaemia in refractory angina pectoris

Adrian Gonon1,2a, Arina Richter3a,4, Ingemar Cederholm3a,4, Jehangir Khan2b, Jacek Novak†1b,2a, Micha Milovanovic3b, Birgitta Janerot-Sjoberg1a,2a+c.

1Karolinska Institutet, (Departments of 1aClinical Science, Intervention & Technology; and 1bLaboratory Medicine) and 2Karolinska University Hospital (Departments of 2aClinical Physiology; 2bMedical Physics; and 2cMedical Technology), Stockholm, Sweden

3Linköping University (Departments of 3aMedicine & Health; and 3bWelfare and Care) and 4Linköping University Hospital (Heart Centre), Linköping, Sweden.

Corresponding author
Adrian Gonon, MD, PhD
Department of Clinical Physiology C1-88
Karolinska University Hospital Huddinge
141 86 Stockholm, Sweden
adrian.gonon@ki.se

Keywords: Refractory angina pectoris, thoracic epidural analgesia, placebo-controlled study, quality of life, anti-ischaemic effect, myocardial scintigraphy

Running title: TEDA and stress-induced ischaemia

† Deceased Apr 29, 2014
Abstract

**Background:** Thoracic epidural analgesia (TEDA) is offered to patients with refractory angina pectoris. In those patients our primary objectives were to evaluate the influence on quality of life (base for power analysis) and if TEDA with bupivacaine during one month counteracts stress-induced myocardial hypoperfusion, increases physical performance and improves quality of life.

**Methods:** Patients with refractory angina and reversible hypoperfusion as demonstrated by myocardial perfusion images (MPI) were randomized to one-month treatment with TEDA either with bupivacaine (B-group, n=9) or saline (P-group, n=10) in a double blind fashion. MPI and bicycle ergometry were repeated after 1 month. Symptoms, nitrate consumption and quality of life were followed weekly.

**Results:** At 1 month, there was no change in either MPI at rest or MPI during bicycle stress (hypoperfused myocardium: before TEDA 20,7% (6,5/34,9) and at 1 month 22,9% (5,6/40,2); n=10) for patients in the saline group in contrast to bupivacaine with reduced exertional-induced myocardial hypoperfusion at 1 month (before TEDA 31,8% (11,8/51,7) and exercise at 1 month 21,2% (3,5/39,0); n=9; p <0.01). Physical performance did not improve. Both groups exhibited similar results and time pattern (p<0.05-0.001) with reduced consumption of nitrates, fewer attacks of angina and an increased quality of life.

**Conclusions:** In refractory angina, TEDA with bupivacaine inhibits myocardial ischaemia in contrast to TEDA with saline. Regardless of whether bupivacaine or saline is applied, TEDA continuously for 1 month improves the quality of life and reduces angina, even when physical performance remains low. A significant placebo effect has to be considered.
1 Introduction

Angina pectoris is typically treated pharmacologically or by coronary artery interventions such as percutaneous angioplasty or open coronary bypass surgery. Chronic, refractory angina pectoris is caused by coronary insufficiency when coronary artery disease cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. When coronary interventions are not possible, are too risky, or severe symptoms persist after interventions, thoracic epidural analgesia (TEDA) is an alternative treatment. It has been used with positive effects on symptoms and quality of life without serious adverse effects. The patient category with refractory angina is increasing with associated poor quality of life, repeated hospitalizations and high healthcare consumption. The placebo effect of invasive treatment might however be huge, as shown with direct myocardial revascularization where similar substantial improvement was seen after both sham and active procedures. The positive reported effects of TEDA are, however, striking and, in addition to the analgesic effect from local anaesthetics, an anti-ischaemic and oxygen deficiency protective myocardial effect from TEDA has been suggested and supported. A local anaesthetic blockade at the level of the 2nd-5th thoracic sympathetic ganglia is considered to inhibit the sympathetic nervous system and adverse effects on the heart, where both $\alpha_1$- and $\alpha_2$- adrenergic receptors mediate epicardial and micro-vascular vasoconstriction and initiate potentially myocardial ischemia. Normally, physical or mental stress dilates the coronary arteries but stenotic coronary arteries react paradoxically with contraction. During TEDA, a
decrease in heart rate and cardiac pressure work is reported with a concomitant reduction in myocardial oxygen demand. Additionally, an increased diameter of the coronary artery stenosis and improved left ventricular diastolic and/or systolic function are described, both at rest and during exercise in patients with coronary artery disease. The evidence of positive effects from beta-adrenergic receptor blockers, relieving symptoms and prolonging life in patients with coronary artery disease and heart failure, strengthens the hypothesis of sympathetic influences, although the mechanisms remain partly unknown. We were interested in evaluating whether the potential anti-ischaemic effect of TEDA was detectable in a clinical setting as well as examining the role of local anaesthetics, and therefore designed a placebo-controlled study.

Our hypothesis (primary objective) was that home self-TEDA treatment with local anaesthetics (bupivacaine) in these patients increases quality of life and reduces the ischemic myocardial burden and protects against exercise-induced myocardial ischaemia in patients with refractory severe angina and that this can be detected by myocardial scintigraphy before or at a controlled workload after one month's treatment when compared to before treatment. Secondary supporting outcomes considered were increased work capacity at bicycle ergometry, decreased angina, and less anti-anginal medication consumption. Treatment safety and healthcare consumption over one month were additionally evaluated. The control group constituted from patients who went through the same protocol but were randomized to treatment with thoracic epidural saline, herein after referred to as placebo.

2 Material and Methods
This randomized, prospective, double-blind study was performed at Linköping Heart Centre, University hospital, County Council of Östergötland, Linköping, Sweden after receiving ethical and regulatory approval in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki. Before patient inclusion, approval was obtained from the Linköping University Hospital Local Ethics Committee (20001010, Dnr 00-230), from the local Radiation Safety/Isotope Committee (20001016: Myocardscintigrafi TEDA) and from the Swedish Medical Products Agency (20010920, LMV Dnr 151:1251/00). All patients gave informed written consent to participate before inclusion. Consecutive patients with refractory angina, optimized anti-angina medical treatment and without contraindications, who were scheduled for TEDA treatment between 2002 until 2006, were considered for the study. Inclusion criteria included age above 18 years, and the possibility to adequately contribute (e.g. no dementia, bleeding disorder, paralysis or drug abuse). All patients underwent myocardial scintigraphy and those who did not present reversible perfusion defects were excluded from the study (for details please see Figure 1). The study population was randomised either to active (B-group: Bupivacaine, Marcaín® 2.5mg/ml, 2-5ml, Astra Zeneca) or placebo (P-group: sodium chloride 0.9%, 2-5ml) treatment for 1 month. A prospective, double blind, parallel-group design was applied for both treatment and analysis (Figures 1 and 2). The identical syringes with saline or bupivacaine was numbered from the pharmacy and distributed to the patients pseudonymized with the same number for all further analyses. The insertion of thoracic epidural catheter and subcutaneous tunnellation is described elsewhere 10. In brief, the thoracic epidural catheter (Portex 16G Clear Catheter, 3 lateral eyes SIMS Portex Ltd., Hyde, Kent, UK) was inserted percutaneously 5-7 cm into the epidural space at thoracic level 2, 3, 4 or 5 using the “loss-of-resistance” technique. The catheter was tunnelled subcutaneously from the back to the front, where it emerged
from the skin, was sutured and covered by a plastic adhesive film, providing easy access for the patients to self-administrate epidural injections. Patients on medication with clopidogrel had to discontinue the medication for five days before insertion of the catheter and warfarin was discontinued until an INR <1.4 was reached. Both medicines were reinstated at the day of insertion. The injected volume at insertion was determined from sensibility reduction in thoracic dermatomes 2-5 using bupivacaine in all patients. On the first 2 days, blinded injections of placebo or bupivacaine were performed 4 times daily with the same amount as at insertion, following the applied clinical routine based on previous extensive experience. Subsequently, injections were twice daily at defined time points, with additional injections optionally in the event of nitroglycerine-resistant chest pain, maximized to once an hour.

The number of regular doses could be increased to a maximum of 6 per day at defined time points if patients’ symptoms were not sufficiently relieved. If non-relief of symptoms persisted, in spite of 6 regular applications, the patients were withdrawn from the study and the drug code broken. A clinical examination of cardiac and catheter status including routine lab parameters (accredited lab ISO/IEC 17025:2005) was performed before starting TEDA treatment. Clinical check-ups were repeated one week and one month after thoracic epidural catheter insertion, and as needed. After one month, all patients received open bupivacaine treatment and were scheduled for a clinical check-up at 3 months.
2.1 Myocardial ischaemia and non-perfused myocardium

Single-photon emission computed tomography (SPECT, myocardial scintigraphy) is the gold standard of today to diagnose myocardial perfusion deficit at rest and ischaemia at stress. Before starting TEDA treatment, a 2-day myocardial scintigraphic SPECT examination was performed. On Day 1, during a maximal semi-supine bicycle ergometry test including electrocardiogram (ECG), 99mTc-tetrofosmin (Myoview®, 5MBq/kg, GE Healthcare) was injected intravenously (i.v.) 1-2 minutes before peak stress. On Day 2, the i.v. injection (7MBq/kg) was repeated at rest. Within 15 minutes after the isotope injection, the patient was placed in the gamma camera (GE Healthcare Millenium VG™) for scanning. After image reconstruction according to the clinical routine, an experienced nuclear medicine specialist visually evaluated the images. Only patients with reversible ischaemia were included and randomized to either active bupivacaine or placebo treatment. Patients without reversible defects were excluded and clinically re-judged.

The semi-supine stress and SPECT protocols were repeated in an identical manner after 1 month of thoracic epidural treatment. We wanted to evaluate the long-term and potential longlasting effect of TEDA and the ethical committee approved only one month with patient on saline/placebo, due to the previous reported favourable effect with bupivacaine. This was approved only if all study patients hereafter were offered open bupivacaine.

SPECT images were blindly evaluated in the Hermes Medical Solutions’ system (Stockholm, Sweden). Hybrid Recon™ was used to reconstruct the images. No attenuation correction was used. After reconstruction, the images were post-filtered in multimodality using a Butterworth filter. The left ventricle was divided into 14 segments.
and quantitative perfusion estimates (Hermes QPSTM) in 5 categories were automatically performed for each segment [0: normal perfusion, 1: 25%, 2: 50%, 3: 75% and 4: 100% reduced perfusion]. The % of non-perfused myocardium was calculated for each left ventricular image, and the results were compared between individuals (stress-rest; before-after) and between groups (active bupivacaine treatment or placebo). A pre-study test was performed where blinded automatic categorization was compared to blinded visual categorization. Visual evaluation performed by an experienced nuclear medicine specialist showed moderate to good agreement with automatic categorization (κ 0.4-0.6). Although the categorization differed somewhat, similar clinical diagnostic results were achieved for all.

2.2 Physical performance

A seated bicycle maximal ergometry with a 12-lead ECG was performed before TEDA treatment. The test was repeated with the same workload 1 month later, within 1 hour from the last bupivacaine or placebo injection. Heart rate, blood pressure, and angina or dyspnoea symptoms were recorded. Maximal exercise capacity was limited by patients fatigue and chest pain.

2.3 Every day angina, quality of life, treatment safety and healthcare consumption

All patients reported continuously on estimated degree of angina, which included information on number of attacks and anti-angina medication (nitrates) consumption. Thoracic epidural catheter function was controlled at clinical check-ups. Additionally,
grading of angina pectoris according to the Canadian Cardiovascular Society (CCS),
functional classification for heart failure according to the New York Heart Association
(NYHA) and the estimated individual quality of life assessed using a visual analogue
scale (VAS) were performed. The consumption of medical care (office visits, hospital
admissions) was analysed from the medical records after 3 months.

2.4 Statistics

A power analysis (90%) was performed on one of two primary goals (increased life
quality) and based on previously published results of our group, suggesting 50 patients
(at least 21 in each group). A personal computer (IBM Lenovo) commercial software
(Prisma, GraphPad Inc., San Diego, CA, USA) was used for statistical analysis. Mean,
standard deviation (SD), standard error of mean (SEM) confidence interval 5-95% were
calculated and one- and two-way ANOVA followed by Bonferroni's multiple comparison
tests or Student's t-test (two-sided paired for comparison of repeated measures,
unpaired for comparison between groups) were used for parametric data, and Chi-
square test for categorical data. A \( p < 0.05 \) was considered as significant.

3 Results

The study was closed before the planned 50 patients were included due to slow
inclusion, changed hospital routines and key persons leave. The included patients gave
high enough power (90%) to reach the primary goal of life quality assessment with
more than 50% placebo effect. 19 patients (10 in the placebo group, 9 in the
bupivacaine group) completed the first month (Figure 1); 3 stopped taking part and
withdrew from the study due to technical problems with the tunnelled catheter and/or
low effect (drug code broken: bupivacaine) and a desire for open treatment. Catheter
problems (dislocation) occurred in another 3 patients in the placebo group during the
placebo-controlled 1-month period; these catheters were replaced within 48 hours. All
19 patients completed the 3-month check-up; 5 catheters were replaced during months
2 and 3. None of the patients needed more than 6 regular doses a day, and no further
drug code was broken during the 3 months.

Randomization outcome (Table 1): The medication of each patient was before
consideration for the study optimized to protect from coronary artery disease and
angina relief. No indication for TEDA was found in unstable patients and the optimized
medication had been evaluated during some time. Only patients with exertional
inducible hypoperfusion on SPECT myocardial perfusion images (MPI) were included
within two weeks in the study. After TEDA was applied medication continued
unchanged. Compared to the placebo group, the bupivacaine group were significantly
more frequently considered for TEDA because the risk with coronary artery
intervention was too high; they were medicated with warfarin; diagnosed with
significant valvular disease; had diastolic dysfunction; and fewer were in sinus rhythm.
More patients in the placebo group had less concomitant cardiac disease; they were
more often considered unsuitable for any coronary intervention, were medicated with
aspirin, and a significantly higher number experienced thoracic epidural catheter re-
implantation due to dislocation or blocking during the 3 months compared to the
bupivacaine group. Serious side effects were not documented in any of the patients.

3.1 Quality of Life (primary goal) (Table 2)
Quality of life-visual analogue scale increased significantly in both groups during 1 month from 33(18/50) to 54(30/78) in the P-group and from 40(19/61) to 48 (25/70) in the B-group ($p < 0.01$). There was no difference between the groups at the different time points when it was assessed.

3.2 Degree of stress induced ischaemia and non-perfused myocardium (Table 3, Fig. 3 A and B)

At inclusion, the degree of hypoperfused myocardium in the placebo group ranged from 2% to 58% at rest and from 16% to 66% at stress. In the active bupivacaine treatment group, the corresponding values were 4% to 57% at rest and 11% to 61% at stress. Patients in the bupivacaine group had initially a significantly higher % of calculated hypoperfused myocardium at stress than the placebo-group ($p=0.006$), while at rest there was no significant difference between the groups ($p=0.11$).

The significant difference in % perfused myocardium between stress and rest ($p<0.01$) persisted at 1 month in the placebo group, indicating residual exercise-induced myocardial ischemia. Stress and rest showed no difference in the extent of hypoperfused myocardium before and after 1 month of treatment in the placebo group. In the bupivacaine group after 1 month, however, stress did not induce an increase in % calculated perfused myocardium ($p=0.89$ compared to rest). The increase in hypoperfused myocardium at stress after 1 month of treatment was inhibited by bupivacaine when compared to stress before TEDA ($p<0.01$). No difference in % non-perfused myocardium was seen at rest after 1 month compared to before TEDA in the bupivacaine group ($p=0.62$)
3.3 Physical performance.

In both groups the maximal performance was generally low. It did not differ significantly between or within the patient groups, neither before TEDA (P-group: 96 W (75/116); B-group 81 W (66/96)) nor at 1 month (P-group: 97 W (81/114); B-group 78 W (67/89)).

Neither did the maximal heart rate (P-group : before 108 bpm (93/123) and 1 month 108 bpm (98/119); B-group: before 104 bpm (92/115) and 1 month 96 bpm (86/107)) or maximal systolic blood pressure (P-group : before 167 mmHg (146/188) and 1 month 156 mmHg (135/176); B-group: before 140 mmHg (125/154) and 1 month 132 mmHg (119/145)) change during the tests. The experience of chest pain related to workload showed a non-significant, slight decline in both groups, even though they received a regular active dose of bupivacaine within one hour before the ergometry test.

3.4 Degree of angina pectoris, nitrate consumption and treatment safety (Table 2)

The number of daily angina attacks was similar in the placebo and bupivacaine groups at inclusion, decreased significantly in both groups during the coming weeks, but at week 4 the bupivacaine group had a higher number of attacks than the placebo group. The consumption of nitrates was similar in both patient groups pre-study, decreased significantly but was higher in the bupivacaine group at both the 4-week and 3-month follow up. Accordingly, their numbers of extra injections were higher than the placebo-group at 3 months. The changes occurred mainly during the first 4 weeks in both groups and persisted during the coming 2 months when all received active bupivacaine treatment. A similar significant pattern was seen for angina, as estimated by the patients according to the CCS. No such pattern was seen in heart failure symptoms in either of
the groups as evaluated by NYHA classes. Serious side effects were not documented in any of the patients.

3.5 Healthcare consumption over 3 months

In both groups, the only hospitalization registered during the 3 months was for re-implantation of dislocated thoracic epidural catheters.

4 Discussion

This study showed that TEDA in refractory angina increased quality of life but the most novel finding of this study is that bupivacaine applied prior to physical exercise inhibits inducible myocardial ischaemia, but does not result in higher performance with bicycle ergometry. Thoracic epidurally applied saline in the control group did not show this inhibiton but had similar effects on quality of life as TEDA with bupivacaine that were earlier reported by non-placebo-controlled studies \(^3,10\) with treatment of bupivacaine alone. Experience of angina attacks, as indicated by consumption of short-acting nitroglycerine per day, decreased in a similar pattern, irrespective of treatment with saline or bupivacaine.

SPECT demonstrated that neither TEDA with saline (placebo) nor bupivacaine influenced myocardial perfusion at rest after the short observation period of one month. The burden of infarction and area of hypoperfusion remained unchanged in spite of frequent symptoms of angina in both groups. Patients with refractory angina pectoris in the placebo group had a non-changing and reproducible ischemic burden during the
same exercise workload repeated one month later. In contrast, the important finding of
this study was that TEDA with bupivacaine significantly ($p<0.01$) improved myocardial
perfusion during exercise as evaluated by blinded semi-quantitative automatic
myocardial SPECT imaging. Bupivacaine, stated to have an analgesic effect in the
epidural space of the thoracic 2-5 dermatomes for about 95 ± 6 minutes $^8$, was
administered 30-60 minutes before exercise and inhibited significantly the decreased
uptake of radioisotope in the myocardium during stress. This is in contrast to the earlier
observation assessed by coronary angiography $^{12}$ where TEDA with bupivacaine
increased only the luminal diameter of a stenosis without influencing the post-stenotic
arterioles and total myocardial blood flow in the jeopardized myocardium. On the other
hand, it is a well-known physiological phenomenon that post-stenotic arteries are kept
at maximal relaxation to compensate for a flow-limiting proximal stenosis $^{13}$ and
heterogeneous blood flow in the microvasculature in the injured myocardium might be
heterogeneously distributed $^{14}$.

Earlier studies reported that TEDA in patients with coronary artery disease improved
global and regional left ventricular function during stress-induced myocardial ischaemia
$^8$ and partly normalizes the myocardial blood flow response to sympathetic
stimulation$^{15}$. To elucidate any possible improved physical performance, the patients
performed bicycle exercise tests for SPECT before and 1 month after initiation of TEDA.
In this study, the limited number of patients and low maximal workload restrict the
conclusions that all patients, independent of treatment, did not perform better and were
mainly limited by chest pain and dyspnoea; nonetheless, this is in line with a recent
study which appears to confirm that patients with stable angina pectoris do not improve
exercise capacity after percutaneous coronary intervention for a single severe coronary
stenosis when compared to optimal medical treatment alone $^{16}$.
Patients with refractory angina pectoris have an advanced cardiac disease, a concomitant higher fatality rate and a markedly impaired quality of life, compared with patients who are eligible for any kind of coronary interventions. Alternative treatments to relieve chest pain, increase quality of life and physical performance have been tested in patients with refractory angina, and earlier studies have shown a favourable effect on refractory angina pectoris with applied spinal cord stimulation, trans-myocardial laser revascularisation or TEDA, but nevertheless, most of these studies lacked a proper control group with an attached device or surgical procedure. Leon et al showed that the surgical procedure per se resulted in a slight improvement of angina symptoms over a 6-month follow-up, and there was no difference compared to the group receiving myocardial laser channels. These results and our study provide evidence that the efficiency and benefit of any invasive treatment regime has to be proven by comparison with a proper control group and must provide benefit beyond the expectation of a surgical sham procedure.

A limitation of the study is the low number of patients included due to the alternative treatments offered, and the cumbersome handling of the thoracic epidural catheter. The resulting skewed randomisation among included patients constrains comparison between groups, and only TEDA with bupivacaine showed a small but significant decrease in stress-induced ischemia that was not seen with the placebo. The dominant main effect in both groups is reduced symptoms which was substantial in the placebo group. Such a substantial placebo effect will easily mask a modest anti-ischaemic effect of bupivacaine when used for clinical evaluations, making it hard to prove symptomatically even if larger cohorts were studied. Inducible ischaemia in smaller areas might not be detected by SPECT due to the inherent low spatial resolution, but neither can it be expected that patients with a great burden of coronary artery disease
would perform differently during exercise tests with this small increase in myocardial perfusion during stress. The skewed randomisation could also explain the higher dislocation of the TEDA catheters in the placebo group if those patients were more physically active.

Anti-anginal medication was kept without any changes in all patients beside clopidogrel and warfarin those were discontinued between the first SPECT-MPI and insertion of the epidural catheter. No bleeding adverse effects were recorded. This is in accordance with previous studies\textsuperscript{3,10} where longterm TEDA has been safe to apply also in anticoagulated patients. Medication of non-vitamin K antagonist oral anticoagulants should be interrupted since there are no reports about the safety in patient with longterm treatment with epidural catheter. The continuously invasive, potentially hazardous together with cumbersome handling of TEDA have given priority to more non-invasive or single invasive procedures. Our study however shows that TEDA still is to be considered if disabling angina remains, necessitating proper knowledge, handling and management. Further studies are needed to show if the effects of new technologies and/or medication are comparable.

In conclusion, antianginal treatment of refractory angina with thoracic epidural catheter is safe; it improves the quality of life, decreases angina attacks and the daily need for nitrates, and does not increase healthcare consumption, irrespective of whether bupivacaine or saline is applied. In these patients with both permanent and stress-induced myocardial perfusion deficits, the presence of bupivacaine in the epidural level of 2\textsuperscript{nd}-5\textsuperscript{th} thoracic sympathetic ganglia reduces stress-induced myocardial ischaemia and angina but with no effects on physical performance as evaluated by a bicycle stress test.
Acknowledgments

Financial support was awarded by the County Council of Östergötland and strategic grants by Karolinska Institutet. We thank MD Eva Olsson at the Department of Clinical Physiology, Linköping Heart Centre, for immediate evaluation and confirmation of ischaemic response on myocardial scintigraphy for potential candidates.

Conflict of interest

None declared.
Reference list


Tables

Table 1. Patient demography and description of the two randomized groups at study inclusion [mean (SD)].

Abbreviations: Redo (Catheter replaced due to dislocation or blockage), LBBB (left bundle branch block), EF (left ventricular ejection fraction), ASA (acetyl-salicylic acid), ACEI (angiotensin-converting enzyme inhibitor), COPD (Chronic obstructive pulmonary disease).

Table 2. Symptoms and drugs in the two randomised groups during the study [mean (SD)].

Abbreviations: CCS (angina according to the Canadian Cardiovascular Society); NYHA (dyspnoea according to the New York Heart Association functional classification for heart failure); Injections (extra bupivacaine or placebo); VAS (subjective quality of life esteemed 0-100 from a visual analogue scale); AP (angina pectoris attacks), Nitrates (oral nitroglycerin or glyceryltrinitrat); LVEDD (left ventricular end-diastolic diameter).
Figures

**Figure 1** Flow Diagram

**Figure 2** Study protocol

**Figure 3 A and B.** Automatically determined hypoperfused myocardium expressed in percent of the left ventricle during rest and exercise single photon emission tomography myocardial perfusion imaging (SPECT-MPI) before and after one month with TEDA in the (a) placebo-group and in the (b) bupivacaine-group. Data presented as mean(S.E.M.). Significance levels are indicated ** p<0.01, *** p<0.001.
<table>
<thead>
<tr>
<th>DEMOGRAPHY</th>
<th>Placebo (n=10)</th>
<th>Bupivacaine (n=9)</th>
<th>ALL (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72 (10)</td>
<td>75 (10)</td>
<td>74 (10)</td>
</tr>
<tr>
<td>Females</td>
<td>20%</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86 (11)</td>
<td>78 (14)</td>
<td>82 (13)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174 (5)</td>
<td>173 (8)</td>
<td>173 (6)</td>
</tr>
<tr>
<td>Inoperable</td>
<td>100%</td>
<td>67%</td>
<td>89%</td>
</tr>
<tr>
<td>Too high risk</td>
<td>0%</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>Redo</td>
<td>50%</td>
<td>22%</td>
<td>37%</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>90%</td>
<td>44%</td>
<td>68%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10%</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>3-vessels disease</td>
<td>80%</td>
<td>67%</td>
<td>74%</td>
</tr>
<tr>
<td>LBBB</td>
<td>0%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>0%</td>
<td>38%</td>
<td>17%</td>
</tr>
<tr>
<td>Normal EF</td>
<td>25%</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>EF &lt;40%</td>
<td>50%</td>
<td>60%</td>
<td>53%</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>11%</td>
<td>80%</td>
<td>38%</td>
</tr>
<tr>
<td>Drug</td>
<td>0%</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0%</td>
<td>33%</td>
<td>16%</td>
</tr>
<tr>
<td>Betablockers</td>
<td>100%</td>
<td>89%</td>
<td>95%</td>
</tr>
<tr>
<td>Nitrates</td>
<td>90%</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Calciumblockers</td>
<td>80%</td>
<td>78%</td>
<td>79%</td>
</tr>
<tr>
<td>ACEIs</td>
<td>70%</td>
<td>44%</td>
<td>58%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>70%</td>
<td>33%</td>
<td>53%</td>
</tr>
<tr>
<td>Statins</td>
<td>90%</td>
<td>89%</td>
<td>89%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30%</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td>Steroids</td>
<td>20%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>40%</td>
<td>22%</td>
<td>32%</td>
</tr>
<tr>
<td>COPD</td>
<td>20%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Smokers</td>
<td>10%</td>
<td>22%</td>
<td>16%</td>
</tr>
<tr>
<td>X-smokers</td>
<td>60%</td>
<td>67%</td>
<td>63%</td>
</tr>
<tr>
<td>SYMPTOMS &amp; DRUGS</td>
<td>Placebo (n=10)</td>
<td>Bupivacaine (n=9)</td>
<td>ALL (n=19)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>CCS before</td>
<td>3.3 (0.5)</td>
<td>3.4 (0.5)</td>
<td>3.4 (0.5)</td>
</tr>
<tr>
<td>CCS at 2 w</td>
<td>2.6 (0.5)</td>
<td>2.3 (0.9)</td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td>CCS at 1m</td>
<td>2.1 (0.7)</td>
<td>2.6 (1.0)</td>
<td>2.3 (0.9)</td>
</tr>
<tr>
<td>NYHA before</td>
<td>1.8 (0.9)</td>
<td>1.7 (0.9)</td>
<td>1.7 (0.9)</td>
</tr>
<tr>
<td>NYHA at 1m</td>
<td>1.8 (0.9)</td>
<td>1.7 (0.9)</td>
<td>1.7 (0.9)</td>
</tr>
<tr>
<td>Injections/w at 1w</td>
<td>19 (3.6)</td>
<td>18 (4.0)</td>
<td>18 (3.7)</td>
</tr>
<tr>
<td>Injections/w at 2w</td>
<td>17 (5.0)</td>
<td>19 (5.8)</td>
<td>18 (5.4)</td>
</tr>
<tr>
<td>Injections/w at 3w</td>
<td>17 (4.3)</td>
<td>21 (6.3)</td>
<td>19 (6.0)</td>
</tr>
<tr>
<td>Injections/w at 1m</td>
<td>17 (4.6)</td>
<td>21 (7.0)</td>
<td>18 (5.3)</td>
</tr>
<tr>
<td>VAS before</td>
<td>40 (25)</td>
<td>26 (7)</td>
<td>33 (19)</td>
</tr>
<tr>
<td>VAS at 4 m</td>
<td>58 (20)</td>
<td>41 (23)</td>
<td>50 (22)</td>
</tr>
<tr>
<td>AP/w before</td>
<td>8 (11)</td>
<td>15 (13)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>AP/w at 2 w</td>
<td>7 (6)</td>
<td>13 (8)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>AP/week at 1 m</td>
<td>5 (4)</td>
<td>14 (11)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Nitrates/w before</td>
<td>26 (13)</td>
<td>25 (13)</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Nitrates/w at 2 w</td>
<td>11 (10)</td>
<td>10 (10)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Nitrates/w at 1 m</td>
<td>7 (6)</td>
<td>11 (16)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>LVEDD before</td>
<td>53 (10)</td>
<td>52 (7)</td>
<td>53 (6)</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>LVEDD 1 m</td>
<td>53 (6)</td>
<td>51 (8)</td>
<td>53 (10)</td>
</tr>
</tbody>
</table>
Assessed for eligibility (n=27)

Excluded (n=5)
- Not meeting inclusion criteria (n=5)
- Declined to participate (n=0)
- Other reasons (n=0)

Randomized (n=22)

Tunneled TED catheterisation (n=22)

Allocated to Placebo (n=11)
- Received allocated intervention (n=10)
- Did not receive allocated intervention (n=0)
- Redo due to cath. dislocation (n=0)

Lost to 4w follow-up (n=1)
- Wish of open treatment (n=1)
- Discontinued intervention (n=0)

Analysed (n=10)
- Excluded from analysis (n=0)

Allocated to Bupivacain (n=11)
- Received allocated intervention (n=11)
- Did not receive allocated intervention (n=0)
- Redo due to cath. dislocation (n=3)

Lost to 4w follow-up (n=2)
- Broken code because of low effect (n=1)
- Cath. dislocation – did not want new (n=1)
- Discontinued intervention (n=0)

Analysed (n=9)
- Excluded from analysis (n=0)
Before 1 month

Hypoperfusion % of Left Ventricle

Rest

Exercise

N/S

N/S

***

**

**

0

10

20

30

40

50

Before

Before

1 month

1 month

Hypoperfusion % of Left Ventricle