

High Thoracic Epidural Decreases Perioperative Myocardial Ischemia and Improves Left Ventricle Function in Aortic Valve Replacement Alone or in Addition to CABG Surgery Even with Increased Left Ventricle Mass Index

Abstract

Introduction: High thoracic epidural (HTE) may reduce perioperative tachyarrhythmias, respiratory complications and myocardial ischemia (MI) and it may increase coronary perfusion and myocardial oxygen balance through sympatholysis and pain control. The aim of this study is to investigate the benefit of HTE in patients undergoing aortic valve replacement (AVR) alone or in addition to coronary artery bypass graft (CABG). **Methods:** This prospective randomized controlled study was conducted on 80 patients (40 with increased left ventricular mass index (LVMI) and 40 with normal LVMI) who were equally randomised ($n = 40$) to receive either GA with HTE (HTE group) or GA alone (GA group). Heart rate (HR), mean arterial blood pressure (MAP) and the incidence of ischemic ECG changes were recorded. LV functions (preoperative and postoperative by transthoracic echocardiography and intraoperative by transoesophageal echocardiography) were measured preoperative, intraoperative and till 48 H postoperative. **Results:** There was no significant difference in the baseline values of all measurements. HR and MAP were lower, and LV functions were improved in HTE group intraoperatively and postoperatively. Ischemic ECG changes were significantly lower in HTE group; with 42.9% intraoperative risk reduction (95% CI: 0.195-0.943) and 46.6% postoperative risk reduction (95% CI 0.227-0.952) as compared to GA group. The risk of ischemia was significantly higher in patients with increased LVMI in GA group (2.25 times compared to normal LVMI patients with 95% CI: 1.195-4.236), but it wasn't increased in HTE group. LV functions were significantly improved from the induction to 48 H postoperative in HTE group as compared to GA group. **Conclusion:** HTE reduced the incidence of MI and improved the LV function, even with increased LVM, in patients undergoing AVR alone or in addition to CABG.

Keywords: Aortic valve replacement, coronary artery bypass graft, high thoracic epidural, left ventricular mass index.

Introduction

In aortic valve replacement (AVR), there are many factors which increase morbidity and mortality e.g., geriatric age, previous AVR, renal impairment, low functional class, associated coronary artery disease (CAD), left ventricular (LV) dysfunction, aortic regurgitation (compared to stenosis) and atrial fibrillation.^[1,2]

Increased LV mass index (LVMI) has shown to be an independent predictor for morbidity and mortality in cardiac patients^[2,3] and it is associated with CAD, all-cause mortality, and sudden death.^[4] Increased LVMI has been found in patients undergoing cardiac

surgery as an adaptive mechanism to help to limit systolic wall stress and to preserve ejection fraction (EF) in patients with ventricular pressure or volume overload.^[4]

Recently, outcome after cardiac surgery has been improved because of advances in anaesthesia, surgery, cardiopulmonary bypass (CPB), and postoperative care.^[4,5]

High thoracic epidural (HTE) may reduce perioperative tachyarrhythmias, respiratory complications and myocardial ischemia (MI). Also, HTE may increase coronary perfusion and myocardial oxygen balance and it allows early extubation through sympatholysis and excellent pain control.^[6]

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Although several studies have been published to evaluate HTE in cardiac surgery, there is still controversy whether the HTE decreases postoperative morbidity after cardiac surgery.^[6-12] The purpose of this study is to update and explore the impact of HTE with general anaesthesia (GA) in patients undergoing AVR alone (isolated or mixed aortic valve lesions) or in addition to coronary artery bypass graft (CABG) surgery, with normal or increased LVMI.

Methods

This prospective randomized controlled study was conducted after the ethical committee approval and obtaining written informed consent from all patients. Clinical trial registry no is NCT03719248. Eighty patients between 65 and 75 years of age with American Society of Anesthesiologist (ASA) physical status II and III scheduled for elective AVR (for isolated or mixed aortic valve lesions) alone or in addition to CABG were enrolled in this study in Cardio-thoracic Surgery Department at Tanta University Hospital from January 2017 to December 2018.

Exclusion criteria were: emergency cases, EF <30%, MI within the last 4 weeks, severe pulmonary or arterial hypertension and contraindications for HTE (aPTT >45 s, INR >1.4, platelet count <80,000 cell/mm³, administration of clopidogrel within 7 days before surgery and the administration of platelet glycoprotein IIb/IIIa inhibitors). We did not exclude patients who received low molecular weight heparin or aspirin below the dosage of 160 mg per day.

All patients were evaluated with full history (including cardiac symptoms e.g., dyspnoea, orthopnoea), general examination (including weight and height and other systems), cardiac examination, extended echocardiographic imaging and investigations (complete blood count, liver and kidney function tests, blood sugar, lipid profile, coagulation profile (PT, aPTT, and INR), troponin I level, electrocardiogram (ECG) and trans-thoracic echocardiography (TTE).

Preoperative medical therapy was given until the day of surgery except diuretics and aspirin (discontinued 48 hours before surgery).

Echocardiography

Both TTE and intraoperative transoesophageal echocardiography (iTEE) was done by Philips device (Cx50 – Extreme edition) equipped by transthoracic and transoesophageal echo probes. LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), interventricular septal dimensions (IVSD), posterior wall dimension (PWD), end-diastolic area (EDA) and fractional area change (FAC) were measured then ejection fraction (LVEF) was calculated by the machine. LVMI was calculated (by the formula described by Devereux and Reichek)^[13] and it was considered increased if >134 gm.m² in males and >110 gm.m² in females.

We selected 40 patients with increased LVMI and 40 patients with normal LVMI, then they were equally randomised, using sealed envelope method (40 patients in each group with 20 patients had increased LVMI in each group) to receive either GA with HTE (HTE group) or GA alone (GA group).

A 3 channel Amplitude Modulated Holter ECG (Philips Digitrak XT, Koninklijke Philips Electronics N.N) was attached before the entry to operating room (OR), continued for 48 hours post-operatively and analysed for MI (based on the criteria of horizontal or down-sloping ST-segment depression >1 mm below the baseline for at least 1 minute).

iTEE was performed by a cardiac anaesthesiologist (with experience of at least 3 years) immediately preoperatively, after induction of general anaesthesia, before and after bypass and after the haemodynamics had been stabilized and according to ASE/SCA guidelines.^[14,15]

Anaesthetic management

One hour before transferring to the OR, patients received 1 µg.kg⁻¹ fentanyl, then they were transferred to the waiting area, where peripheral venous access and radial arterial cannula were established, and ECG monitoring was initiated in leads II and V₅. In HTE group, an epidural 19-gauge catheter (B | Braun®, Melsungen AG) was inserted at the level of the T3–T4 intervertebral space and advanced 4 cm in the attempt to reach the T1 vertebral body. Then crystalloid 7 mL.kg⁻¹ was administered over 20 minutes. Epidural 0.5% bupivacaine 0.1 mg.kg⁻¹.H⁻¹ with fentanyl 1 µg.kg⁻¹.H⁻¹ were infused till induction of GA. The level of blockage was assessed by a pinprick.

All the patients were monitored with pulse oximeter, non-invasive and invasive arterial blood pressure, capnogram, temperature probe and five leads ECG with ST-segment analysis.

After that, patients were transferred to the OR where GA was induced intravenously, in both groups, with fentanyl (2 µg.kg⁻¹), propofol (1–1.5 mg.kg⁻¹), and cisatracurium (0.15 mg.kg⁻¹) and maintained with an infusion of propofol 3–5 mg.kg⁻¹.H⁻¹ and cisatracurium 0.03 mg.kg⁻¹ every 20 min. Epidural continuous infusion of bupivacaine 0.06 mg.cm⁻¹.H⁻¹ and fentanyl 1 µg.cm⁻¹.H⁻¹ was done for 48 H after the operation.

Surgery

All patients had median sternotomy, a closed CPB system was used, and myocardial protection was done with antegrade crystalloid cardioplegia. Hypotension is defined as 30% decrease in MAP in comparison with basal levels, or MAP ≤65 mmHg for ≥5 minutes and it was treated with a continuous infusion of norepinephrine 0.01-0.04 µg.kg⁻¹.min⁻¹. Immediately before insertion of the arterial cannula into the aorta, 300 U.kg⁻¹ heparin

was given with subsequent doses to maintain an activated clotting time >450 s. Moderate hypothermia (32°C) was maintained during CPB.

After discontinuation of CPB, protamine sulphate 1 mg for every 100 U of heparin was administered. Intensive care (ICU) admission was done after the operation. In HTE group, postoperative additional analgesic drugs were not required and no neurological manifestations (radicular pain, paraesthesia, and temporary or permanent paralysis) were found until discharge from the ICU. In GA group, patient-controlled analgesia (PCA) was done by IV morphine pump for 48 H using 1-mg bolus dosing with a 3-min lockout period.

Measurements

HR and MAP were measured pre-operative, intraoperative (mean value) and 15 min, 2, 4, 12, 24, 36, 48 H postoperative. Plasma concentrations of troponin I was measured preoperatively after induction of anaesthesia, before, after bypass and at 6, 12, 24 and 48 H, postoperatively. ECG, troponin level and echocardiography parameters were measured pre-operative, intraoperative and 12, 24, 48 H postoperative.

The primary outcome is the increase in LVEF and the secondary outcomes are the incidence of perioperative ischemia and improvement of other LV functions.

Statistical analysis

Using Minitab[®] 17.1.0 Statistical Software, the sample size is at least 34 case in each group by the following criteria: expected mean increase in LVEF (the primary

outcome) is 8.25 (15%) with HTE, common SD (9.25) according to a previous study,^[3] group ratio 1:1 with 0.05 alpha error and 95% power of the study. 6 cases were added for dropout.

Statistical analysis was done by SPSS 25 (SPSS Inc., Chicago, IL, USA). Normality of data was checked with Shapiro-Wilks test. Numerical variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing T test. Categorical variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. *P* value <0.05 was considered significant.

Results

Patient flowchart of the study is shown in [Figure 1]. There was no significant difference as regards demographic data, drugs, diseases and duration of anaesthesia [Table 1].

As regards HR and MAP, there was no significant difference between the 2 groups in the baseline values, but there was a significant reduction in HTE group than GA group from the induction to 48 H postoperative [Table 2]. The incidence of hypotension in HTE group was more with females but didn't catch a significance (*P* value 0.091).

Ischemic ECG changes were significantly lower in HTE group; with 42.9% intraoperative risk reduction (95% CI: 0.195-0.943) and 46.6% postoperative risk reduction (95% CI 0.227-0.952) as compared to GA group.

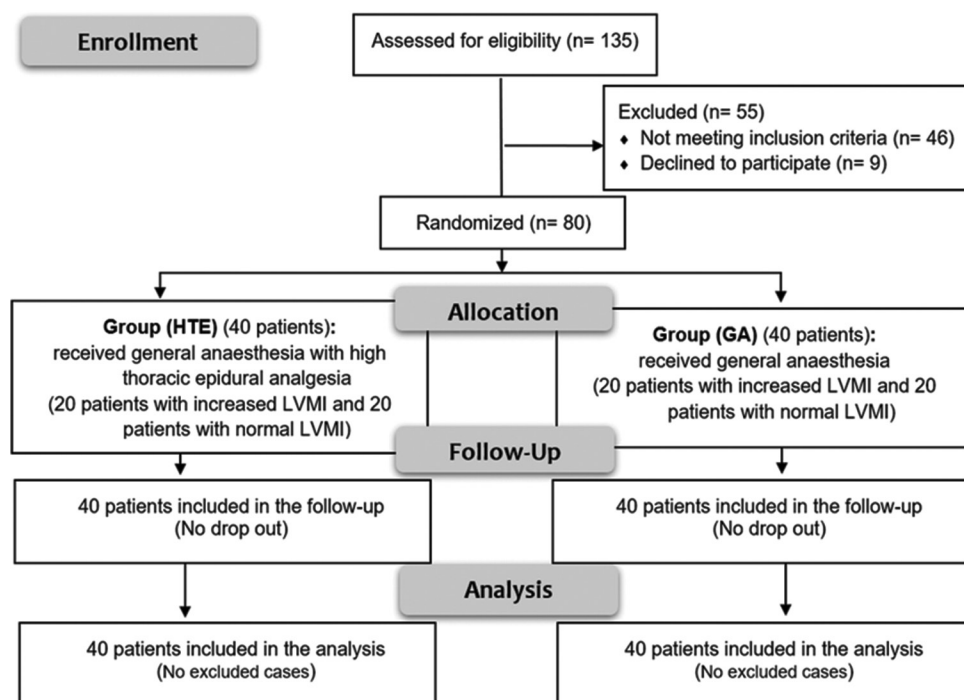


Figure 1: Patient flowchart

The risk of ischemia was significantly higher in patients with increased LVMI in GA group (2.25 times compared to normal LVMI patients with 95%CI: 1.195-4.236), but it wasn't increased in HTE group [Tables 3 and 4].

Table 1: Baseline characteristics of patients in HTE and GA groups

	HTE Group (n=40)	GA Group (n=40)	P
Age (years)	70.1±2.3	69.8±1.92	0.527
Weight (kg)	80.8±11.21	83.10±10.03	0.337
Height (cm)	171.3±4.74	169.6±5.46	0.141
Gender (Male)	29 (72.5%)	27 (67.5%)	0.807
CABG	21 (52.5%)	19 (47.5%)	0.823
Diseases			
Hypertension	31	28	0.611
Diabetes Mellitus	11	14	0.629
Angina	19	23	0.502
Myocardial infarction	7	6	0.762
Hospitalised for CHF	5	5	1
Smoker	22	20	0.823
Peripheral vascular disease	0	0	--
Cerebral vascular accident	0	0	--
Drugs			
Chronic beta blockade	35	33	0.754
Calcium channel blocker	24	25	0.819
Angiotensin ACEI	11	13	0.807
Duration of anaesthesia (min)	236.5±12.6	231.4±11.66	0.064

Numerical data presented as mean±SD and compared by *t*-test, Categorical data presented as frequency and percentage (%) and compared by Chi-square or Fisher's exact test when appropriate.

**P*<0.05 was considered significant

LV functions (LVESD, LVEDD, EDA, LVEF and FAC) were significantly improved from the induction to 48 H post-operative in HTE group as compared to GA group [Table 4].

Discussion

This study showed that the use of HTE along with GA reduced the risk of the incidence of increased LVMI in patients undergoing aortic valve replacement (AVR) alone or in addition to CABG, as compared to that in the group of GA alone. The effect of HTE on LV contractility remains controversial because the myocardial function has been reported to be unchanged,^[10] reduced,^[16,17] or improved.^[6,12] The variability of these results might be due to differences in types of anaesthetics, the level and number of blocked segments, or the methods used to evaluate LV function.

Our study showed that ischemic ECG changes were significantly lower in HTE group as compared to GA group; with 42.9% intraoperative risk reduction and 46.6% postoperative risk reduction. The risk of ischemia was 2.25 times in patients with increased LVMI in GA group compared to normal LVMI patients, but it wasn't increased in HTE group

Our analysis showed significant reductions in HR and MAP from induction to 48 H postoperative in HTE group in patients undergoing AVR alone or in addition to CABG as compared to GA group. This results may be explained by the fact that the HTE attenuates the surgical stress response and improves hemodynamic stability^[18] and recovery after CABG.^[19]

Table 2: Perioperative heart rate (HR) and mean arterial blood pressure (MAP) changes of HTE and GA groups

	Time	HTE Group (n=40)	GA Group (n=40)	P
Heart rate (beat/min)				
Preoperative		89.4±10.8	88.1±11.6	0.605
Intra-operative		69.4±11.7	82.2±10.2	<0.01*
Postoperative	15 min	60.1±9.3	77.2±12.7	<0.01*
	2 h	61.4±9.8	70.6±12.8	<0.01*
	4 h	65.8±9.2	80.0±11.8	<0.01*
	12 h	63.5±9.4	80.3±9.8	<0.01*
	24 h	68.4±12.7	90.2±11.9	<0.01*
	36 h	69.9±11.8	85.5±10.9	<0.01*
	48 h	67.7±13.3	80.8±11.4	<0.01*
Mean Arterial Blood pressure (mmHg)				
Preoperative		101.8±12.2	99.4±12.7	0.391
Intra-operative		85.7±8.6	100.2±11.9	<0.01*
Postoperative	15 min	87.2±12.2	95.3±10.7	<0.01*
	2 h	86.3±11.3	98.6±12.3	<0.01*
	4 h	85.9±12.6	102±10.9	<0.01*
	12 h	86.8±14.2	99.1±10.6	<0.01*
	24 h	89.7±14.6	98.6±12.7	<0.01*
	36 h	87.7±13.3	99.5±11.7	<0.01*
	48 h	88.3±12.8	95.8±12.2	0.009*

Data presented as mean±SD and compared by *t*-test. **P*<0.05 was considered significant

Table 3: Postoperative ischemic ECG comparison between increased and normal LVMI in HTE and GA groups

Group	Subgroup	Ischemia	No ischemia	P
GA group (n=40)	Increased LVMI (n=20)	12 (60%)	8 (40%)	0.022*
	Normal LVMI (n=20)	4 (20%)	16 (80%)	
THE group (n=40)	Increased LVMI (n=20)	3 (15%)	17 (85%)	1
	Normal LVMI (n=20)	3 (15%)	17 (85%)	

Data presented as frequency and percentage (%) and compared by Fisher's exact test when appropriate. *P<0.05 was considered significant

Table 4: Incidence of ischemic ECG changes and LV systolic and diastolic function changes of HTE and GA groups

	Time	HTE Group (n=40)	GA Group (n=40)	P
Ischemic ECG changes				
Preoperative		5 (12.5%)	4 (10%)	0.724
Intra-operative		5 (12.5%)	15 (37.5%)	0.020*
Postoperative		6 (15%)	16 (40%)	0.024*
High troponin level				
Preoperative		0	0	-
Intra-operative		5 (12.5%)	15 (37.5%)	0.020*
Postoperative		6 (15%)	16 (40%)	0.024*
LV systolic and diastolic function Parameters				
LVESD (mm)				
Preoperative		39.7±3	40.5±3.91	0.308
Intra-operative		30.5±3.91	41.50±3.91	<0.001*
Postoperative	12 h	30.5±3.91	44.50±2.91	<0.001*
	24 h	32.5 ± 3.95	43.50 ± 3.01	<0.001*
	48 h	31.5 ± 3.42	45.50 ± 3.91	<0.001*
LVEDD (mm)				
Preoperative		62.27±4.0	61.30±7.4	0.468
Intra-operative		49.2±4.73	66.2±6.73	<0.001*
Postoperative	12 h	45.3±4.62	65.2±6.93	<0.001*
	24 h	46.2 ± 4.53	65.20 ± 5.23	<0.001*
	48 h	45.6 ± 4.69	67.20 ± 6.78	<0.001*
EDA (cm ²)				
Preoperative		31.6±3.9	30.50±3.9	0.211
Intra-operative		20.8±3.9	39.50±3.01	<0.001*
Postoperative	12 h	20.5±3.9	39.50±3.01	<0.001*
	24 h	20.4±3.9	39.50±3.01	<0.001*
	48 h	21.9±3.9	40.50±3.01	<0.001*
LVEF (%)				
Preoperative		54.09±5.4	55.4±6.1	0.312
Intra-operative		60.4±7.4	53.4±6.4	<0.001*
Postoperative	12 h	60.4±5.4	57.2±5.4	<0.001*
	24 h	61.3±7.4	55.5±5.8	<0.001*
	48 h	59.4±6.4	54.6±5.9	<0.001*
FAC (%)				
Preoperative		42.4±6.3	43.22±6.8	0.578
Intra-operative		49±5.4	40.3±7.4	<0.001*
Postoperative	12 h	50.1±4.6	42.3±5.4	<0.001*
	24 h	50.3±5.5	42.3±6.4	<0.001*
	48 h	50.2±5.2	41.3±5.4	<0.001*

Numerical data presented as mean±SD and compared by *t*-test, Categorical data presented as frequency and percentage (%) and compared by Chi-square or Fisher's exact test when appropriate. *P<0.05 was considered significant

LV functions (LVESD, LVEDD, EDA, LVEF, and FAC) were significantly improved intraoperatively and postoperatively till 48 H postoperatively in all HTE group as compared to the GA group. Our finding is similar to that

of the study of Orsinelli and colleagues,^[20] who showed that LV hypertrophy (increased relative LV wall thickness) was associated with greater postoperative morbidity after AVR for aortic stenosis. However, the difference between

our study and that of Orsinelli and his colleagues deserves a comment. We identified the effects of increased LVMI after addition of HTE to GA which reduces the risk of postoperative morbidity.

Increased LVMI and excessive LV hypertrophy are accompanied with impairment of contractility (resulting in congestive heart failure)^[14-17] and decrease in coronary flow reserve.^[12]

This finding is similar to a recent study of Carl-Johan Jakobsen and colleagues^[10] who hypothesized that the addition of HTE to GA would increase cardiac output without compromising MAP or HR during cardiac surgery.

However, the possible benefits of HTE have gained much attention. HTE with local analgesics has beneficial effects in patients with CAD because the cardiac sympathetic (Th1-Th5) blockade by HTE dilates stenotic coronary arteries and attenuates stress-induced MI.^[7,8] In CAD patients, HTE has been evaluated as an adjunctive treatment for refractory chest pain during stable and unstable angina pectoris^[6,12] to improve LV performance and exert a direct anti-ischemic effect.^[6,12]

HTE in cardiac surgery remains controversial in the absence of a sufficiently large, statistically significant effect on mortality, stroke, or MI while possible hazardous complications of HTE, such as epidural hematoma or abscess, must be considered as systematic anticoagulation during CPB may increase the incidence of epidural hematoma by the epidural catheter.^[11]

In the present study, epidural hematoma wasn't found in any case, but this rare complication needs larger sample size to appear. There are few reports^[21-23] on neuraxial hematoma in cardiac surgery linked to HTE.

Limitations of the study

This is a single centre study, hence more such studies should be done in other centres. Our results are not valid to emergency AVRs because we excluded them. In patients with abnormal LV geometry, the LVMI isn't reliable as it is estimated by M-mode echocardiography.

Finally, further studies are needed to investigate the long-term effects of LVMI on outcomes after AVR. Studies with a larger number of patients comparing the outcome of HTE with increased and normal LVMI are needed.

Conclusion

HTE reduced the incidence of MI and improved the LV function, even with increased LVM, in patients undergoing AVR alone or in addition to CABG.

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Conflicts of interest

There are no conflicts of interest.

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