

Research article

Relation of catecholamines with oxidative stress in patients undergoing cardiac surgery before and after endotracheal intubationSah R.K.¹, More K.M.¹, Sathe V.²¹Department of Biochemistry, ²Department of Anesthesia, MGM Medical College, MGM Institute of Health Sciences, Navi Mumbai, Maharashtra, India

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Corresponding author: **Kavita More**. Email: drkavitajadhav2020@gmail.com**ABSTRACT**

Introduction and Aim: Endotracheal intubation is used to maintain the airway open so that oxygen, medicine, or anesthesia can be administered. Anesthesia and surgery boost the release of cross-regulating hormones through physiological responses and psychological stress. There is a strong link between psychological stress and oxidative stress, according to research. The study was aimed to assess the levels of catecholamines (adrenaline and noradrenaline) and oxidative stress before and after endotracheal intubation in patients undergoing cardiac surgery and to study association between them.

Materials and Methods: Total 30 patients undergoing cardiac surgery were enrolled. Blood samples were collected before and after endotracheal intubation. Plasma adrenaline and noradrenaline levels were estimated by ELISA. MDA & SOD were estimated by spectrophotometric method.

Results: The mean levels of plasma adrenaline, noradrenaline and Serum MDA were significantly decreased while Serum SOD were significantly increased after endotracheal intubation as compared to before endotracheal intubation by laryngoscopy in patients undergoing cardiac surgery. Before and after intubation, MDA showed a significant positive association with both nor-adrenaline and adrenaline. SOD activity was negatively correlated with MDA, adrenaline, and noradrenaline before and after intubation.

Conclusion: Elevated levels of adrenaline, noradrenaline, MDA, and lower levels of SOD show that patients are stressed prior to endotracheal intubation, resulting in a stronger stress response, and increased oxidative stress. After intubation, the levels of adrenaline and noradrenaline reduced, indicating a reduction of stress. Our study also shows a link between psychological and oxidative stress. For a better outcome and to avoid subsequent complications, it is preferable to evaluate stress levels and oxidative stress in patients undergoing cardiac surgery before and after endotracheal intubation.

Keywords: Endotracheal intubation; MDA; SOD; adrenaline; noradrenaline.

INTRODUCTION

Tracheal intubation is the insertion of a tube into the trachea through the mouth or nose. It's for patients who need to keep their airway open and their pulmonary breathing under control. It can also be used to regulate ventilation (PaCO₂) and give drugs such surfactant and those for cardiorespiratory arrest (1).

Patients experience significant stress because of laryngoscopy and intubation, either psycho-emotionally due to anxiety of the process or physically due to nociceptive stimulation of pharyngeal, laryngeal, and tracheal receptors during intubation. Patients with a history of cardiovascular illness as well as those with no comorbidities, but notably those in acute situations, may experience unfavorable cardiovascular effects because of the stress generated by tracheal intubation (2). Both surgery and anaesthesia raise the release of cross-regulating hormones (growth hormone cortisol, catecholamines, and glucagon) as a result of physiological and psychological stress, it leads to increase in plasma protein, low levels of potassium, sodium

accumulation, and elevation in glucose levels. Surgical stress increases sympathetic activity and noradrenaline levels, resulting in decreased insulin secretion, uptake of glucose, and increase in gluconeogenesis. This leads to glucose elevation, postoperative infection, and immune system deterioration-related death. Moreover, damage to the neurological, renal, and cardiovascular systems results from these hemodynamic changes (3).

The hypothalamus-pituitary adrenocortical (HPA) and sympathetic adrenomedullary (SAM) neuroendocrine systems are responsible for stress response regulation. Sympathetic activation is followed by activation of the hypothalamo-pituitary axis and increased production of CRH, ACTH, and glucocorticoids after exposure to a stressor (4). A considerable amount of catecholamines is released during stressful situations because of sympathoadrenal discharge. These hormones help the body prepare for a fight or flight response (5). Higher levels of oxidative stress contribute significantly to the aetiology of cardiovascular disease. Lipid peroxidation, which begins in the presence of hydroxyl radicals and results

in the formation of malondialdehyde, directly causes oxidative stress (6).

According to studies, surgery and anaesthetic manipulation-induced sympathetic activation and oxidative stress may be the key factors that cause hypertension, which can activate the sympathetic nervous system and appear to be injurious to patients, particularly neurosurgical patients (4). One of the mechanisms implicated in the pathophysiology of widespread inflammatory reactions is the overproduction of ROS. Oxidative damage is caused by the rapid and massive release of oxygen radicals during reperfusion. To avoid ischemia/reperfusion damage, it would be wise to develop a good prophylactic therapy before critical surgeries or after resuscitation (7).

In view of generation of various stress responses and oxidative stress during endotracheal intubation, and it can lead to adverse cardiovascular complication. This aspect is very rarely addressed; therefore, we have tried to evaluate the levels of catecholamines and oxidative stress before and after endotracheal intubation in patients undergoing cardiac surgery and to assess association between them.

MATERIALS AND METHODS

Study design

This prospective study was conducted in the Biochemistry Department, Department of Operation Theatre and Anaesthesia Technology, in a period of December 2018 – February 2020. The Institutional Ethics committee approval was obtained. Total 30 patients undergoing cardiac surgery were enrolled in the study after obtaining written consent.

Patients in the study ranged in age from 20 to 80 yrs., with ASA physical status grades II and III, elective heart surgery, and either sex. Patients with refusal, emergency surgery, pregnant and lactating women, Patients with conduction abnormalities, persistent pacemakers, low left ventricular function (LVEF 35%), and left main coronary artery disease, any oral cavity lesion, respiratory disease, less than 20 years, women on oral contraceptive, patients with renal, hepatic, or neurological diseases, bleeding diathesis, gastroesophageal reflux disease, delayed gastric emptying, kyphoscoliosis were excluded.

A senior, experienced anaesthetist performed every intubation, who had performed at least 50 intubations using laryngoscope in manikin and at least in 20 patients. Fasting blood samples were collected before and after endotracheal intubation from the patients undergoing cardiac surgery.

All patients were placed on a fast overnight. Patients were given alprazolam 0.5 mg and pantoprazole 40 mg tablets the day before surgery during the pre-anaesthetic examination. After entering the operation

theatre, two peripheral intravenous cannulas were inserted 15 min prior to induction of anesthesia, and IV lines were secured. Premedication was administered - 5 minutes prior to induction of anaesthesia Inj. Midazolam 0.05 mg/kg and Inj. Fentanyl 2 mcg / kg. After discarding 5 millilitres of blood at each timepoint, blood samples were obtained using a different intravenous cannula from a big peripheral vein in order to assess the oxidative stress response and hormonal stress. When significant variations in the catecholamine concentrations were anticipated, central venous catheterization became imperative.

The following schedule was followed for the collection of blood samples

1. Timepoint 1: Five min before to the administration of any induction agent (5 min prior pre-intubation)
2. Timepoint 2: 15 min after tracheal intubation (15 min post intubation)

Estimation of adrenaline was done by ELISA (Kit used: LDN Adrenaline Research ELISA™) and noradrenaline was done by ELISA (Kit used: LDN Noradrenaline Research ELISA™). Kei Sathos method was used for Serum MDA estimation (8) and Marklund and Marklund method was used for SOD estimation (9).

Statistical analysis

The statistical analysis between two groups was evaluated using the Student's 't' test. The results were presented as mean \pm SD. A p-value of less than 0.05 indicates statistical significance. The Pearson correlation coefficient was employed to compare continuous variables. $P < 0.05$ was considered statistically significant.

RESULTS

The mean levels of plasma MDA ($p < 0.0001$), Adrenaline ($p < 0.01$) and Noradrenaline ($p < 0.0001$) were significantly decreased after endotracheal intubation as compared to before endotracheal intubation by laryngoscopy in patients undergoing cardiac surgery (Table 1). Levels of SOD activity were significantly increased ($p < 0.0001$) after tracheal intubation as compared to before tracheal intubation (Table 1).

Significant positive correlation was observed of MDA with adrenaline and nor-adrenaline before and after intubation. SOD activity was negatively correlated with MDA, adrenaline, and noradrenaline before and after intubation (Tables 2 & 3, Fig.1-4).

Table 1: Comparison of plasma adrenaline and plasma noradrenaline, serum MDA and serum SOD levels before and after endotracheal intubation in patients undergoing cardiac surgery

Parameters	Before tracheal intubation (Mean ± SD) (n=30)	After tracheal intubation (Mean ± SD) (n=30)	P- value
Adrenaline(pg /ml)	26.75±10.53	15.75±8.36	p< 0.01
Noradrenaline(pg /ml)	570.62±300.56	247.70±137.69	p< 0.0001
MDA(n moles/ml)	3.18±0.35	2.74±0.27	p< 0.0001
SOD(units/ml)	27.08±3.58	31.86±3.26	p< 0.0001

Table 2: Correlation of catecholamines with oxidative stress markers before intubation

Correlation	Adrenaline	Noradrenaline	MDA	SOD
Adrenaline	-	0.67*	0.52*	-0.63*
Noradrenaline	0.67*	-	0.57*	-0.46*
MDA	0.52*	0.57*	-	-0.53*

p-value: * Significant (p < 0.05)

Table 3: Correlation of catecholamines with oxidative stress markers after intubation

Correlation	Adrenaline	Noradrenaline	MDA	SOD
Adrenaline	-	0.42*	0.54*	-0.46*
Noradrenaline	0.42*	-	0.45*	-0.33
MDA	0.54*	0.45*	-	-0.40*

p-value: * Significant (p < 0.05)

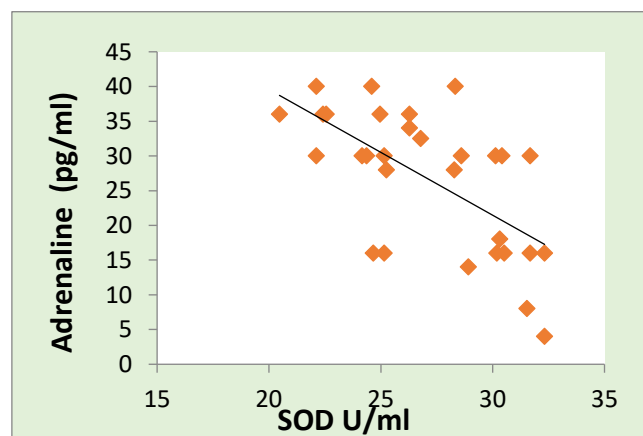


Fig. 1: Correlation between SOD and adrenaline before tracheal intubation

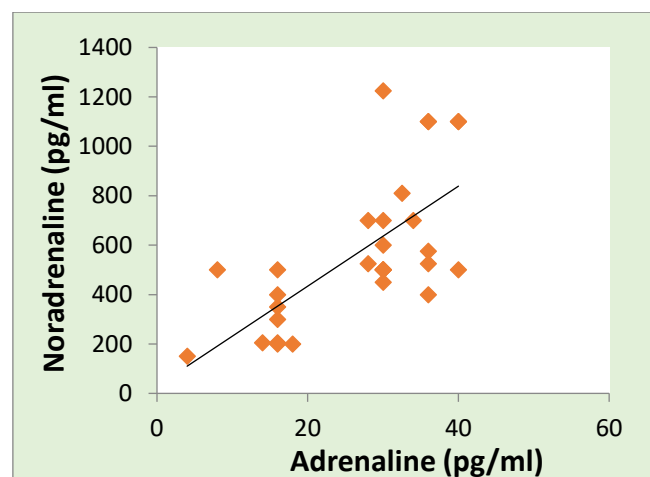


Fig. 2: Correlation between adrenaline and noradrenaline before tracheal intubation

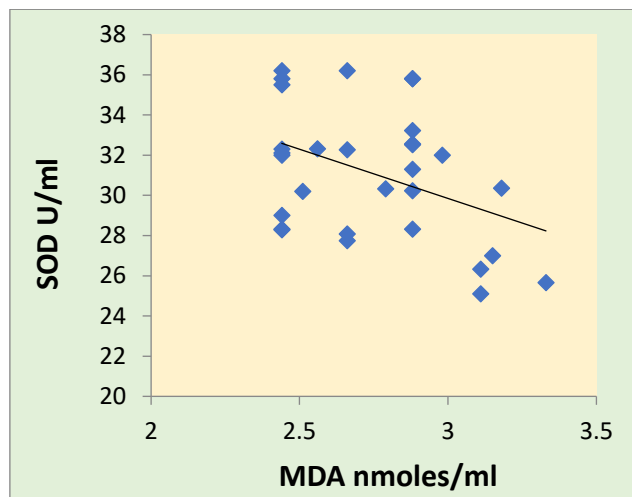


Fig. 3: Correlation between SOD and MDA after tracheal intubation

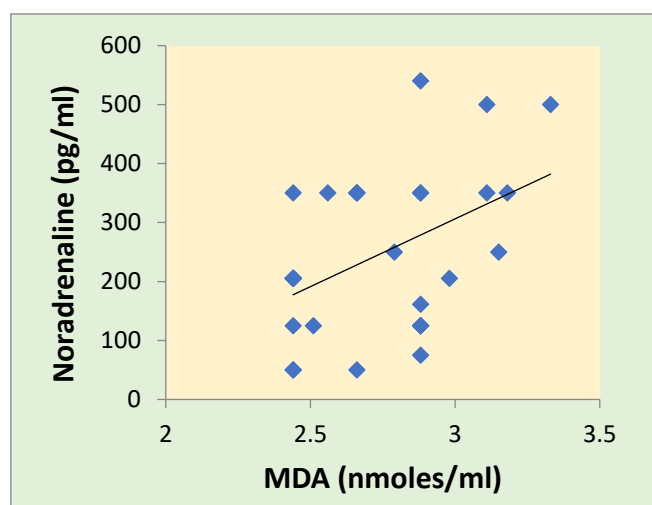


Fig. 4: Correlation between MDA and noradrenaline after tracheal intubation

DISCUSSION

During laryngoscopy and intubation, the patient is put under a lot of stress (10). The stress response makes it easier to make the physiological and metabolic changes needed to deal with threats to the physiological balance. Surgical stress disrupts every homeostatic axis biochemically and physiologically. Acute phase response protein synthesis and secretion, neuroendocrine activation, sympathetic activation, parasympathetic suppression, volume/ baroreceptor regulation, immunological response modulation, and long-term behavioural adaptation are just a few of the changes that take place. (11).

Various studies have shown that when large levels of catecholamines are present, they are oxidized to create oxyradicals and aminolutins. Catecholamine oxidised products have been demonstrated to produce coronary spasms, arrhythmias, and cardiac dysfunction by creating Ca²⁺ handling irregularities in both sarcolemma and sarcoplasmic reticulum, problems in energy generation by mitochondria, and myocardial cell death (12).

Mean values of plasma adrenaline and noradrenaline were significantly reduced (p<0.01) after

endotracheal intubation as compared to before endotracheal intubation by laryngoscopy in patients undergoing cardiac surgery. We also observed that levels of adrenaline and nor-adrenalines are within normal limits. Adrenaline and noradrenaline showed significant positive correlation with MDA and negative correlation with SOD (Tables 2 and 3). Our results are supported by Mustola *et al.*, (13), Russell *et al.*, (14) and Pernerstorfer *et al.*,(15).

Mustola *et al.*, (13) showed that adrenaline concentrations decreased significantly after intubation as compared to before intubation in patients undergoing elective laryngomicroscopy. The mean values of noradrenaline and adrenaline were shown to be lower after endotracheal intubation and the induction of anaesthesia, according to Russell *et al.* (15). However, the alterations did not show statistical significance. Pernerstorfer *et al.*,(15) demonstrated that serum levels of adrenaline reduced slightly after induction and continued unaltered after intubation undergoing elective surgery of the lower limb. Levels of adrenaline and noradrenaline are reduced after intubation that indicates reduction in stress response; this could be due to the stress being

relieved following intubation. It could also be related to the anesthetic medicines used during endotracheal intubation, which can suppress hypothalamic and pituitary hormone release, or the better technique utilized by an experienced anesthetist for laryngoscopy, which can also help to reduce stress.

Levels of serum MDA were significantly decreased, and levels of SOD were increased after endotracheal intubation as compared to before endotracheal intubation by laryngoscopy in patients undergoing cardiac surgery.

Lipid peroxidation process is triggered by free radicals. One of the byproducts of the cells' peroxidation of polyunsaturated fatty acids is MDA. Overproduction of MDA is caused by a rise in free radicals. (16)

Our results for MDA are supported by Tang *et al.*, (4) Song *et al.*, (17) and Zulfikaroglu *et al.*, (18). Tang *et al.*, (4) studied stress response for tracheal intubation in posterior fossa surgery patients. They observed MDA levels were decreased postoperative as compared to preoperative ($P < 0.05$). Further they reported that the decrease of MDA may be due to the use of anesthetics that have antioxidant properties. MDA levels in Group OPLAC (Oro-Pharyngeal airway cap) were significantly lower postoperatively compared to preoperational ($P < 0.015$), as demonstrated by Song *et al.*, (17), which also shows that MDA levels decreased over time in both groups.

In 50 patients undergoing either an open or laparoscopic cholecystectomy, Zulfikaroglu *et al.*, (18) assessed the levels of NO and plasma MDA. These parameters were examined three times before surgery, 24 hours after surgery, and during the procedure. Thirty minutes after the start of the laparoscopic procedure, they found that MDA levels had dropped.

Our results for SOD are supported by Koksai *et al.*, (19) and Luyten *et al.*, (20) showed that the SOD levels were found to be elevated prior extubation as compared to post intubation in patients undergoing abdominal surgery. This rise indicates an antioxidant defence mechanism against oxidative damage. Luyten *et al.*, (20) reported that levels of superoxide dismutase significantly increased during and after surgery as compared to before surgery in the cardiopulmonary bypass surgery patients. Neri *et al.*, (21) concluded that catecholamines, irrespective of their interaction with adrenergic receptors, might cause oxidative damage via reactive intermediates resulting from auto-oxidation, thus representing a significant factor in the pathogenesis of catecholamine-induced cardiotoxicity.

We observed that before endotracheal intubation levels of stress hormones (adrenaline and noradrenaline) are increased, that could be involved in the generation of oxidative stress which is shown

by higher levels of MDA and lower levels of SOD. As stress hormones are decreased after intubation, the level of MDA is decreased, and SOD levels are restored.

Stress hormones (adrenaline and noradrenaline) are raised prior to endotracheal intubation in this study, which could be involved in the formation of oxidative stress, as seen by greater levels of MDA and lower levels of SOD. MDA levels are reduced, and SOD levels are restored as stress hormones are reduced following intubation. The positive correlation of MDA with adrenaline and noradrenaline before and after intubation in our study supports the above findings. Before and after intubation, we found a negative correlation of SOD with adrenaline, noradrenaline, and MDA. These findings reveal a link between hormonal stress and oxidative stress. Future research with a larger sample size is needed to investigate it further.

The limitations of the study are smaller sample size, stress hormone levels should have been measured at multiple times, such as 1 hour, 24 hours after surgery, and during the operation, so that we could have better examined long-term hormonal changes. Consequently, further research is required with bigger sample size and analysis of hormones at different intervals, required to overcome the constraints.

CONCLUSION

Elevated levels of adrenaline, noradrenaline, MDA, and lower levels of SOD show that patients are stressed prior to endotracheal intubation, resulting in a stronger stress response, and increased oxidative stress. After intubation, the levels of adrenaline and noradrenaline reduced, indicating a reduction of stress. Our study also shows a link between psychological and oxidative stress. For a better outcome and to avoid subsequent complications, it is preferable to evaluate stress levels and oxidative stress in patients undergoing cardiac surgery before and after endotracheal intubation.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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