ISOFLURANE PROVIDES BETTER MYOCARDIAL PROTECTION THAN MIDAZOLAM IN PEDIATRIC PATIENTS DURING OPEN HEART SURGERIES

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Abstract:
Objectives:
This study was designed to evaluate the applicability of anesthetic myocardial protection (pre-conditioning and minimization of reperfusion injury) using two anesthetic regimens on plasma levels of cardiac troponin T (cTnT), as a marker of myocardial ischemia, in pediatric patients assigned for surgical correction of congenital heart diseases using cardiopulmonary bypass (CPB).

Patients & Methods:
The study included 60 patients (36 males and 24 females). Patients were randomly allocated in 2 equal groups: Midazolam group received a continuous infusion of midazolam (0.2 mg/kg/hour) and Isoflurane group maintained by an end-tidal concentration of isoflurane of 1-1.5% throughout the operation. Six blood samples were taken for estimation of plasma cTnT levels immediately after induction of anesthesia (S1), 8-hours (S2), 16-hours (S3), 24-hours (S4), 36-hours (S5) and 48-hours (S6) after aortic cross-clamping.

Results:
Plasma cTnT levels estimated after aortic cross-clamping (S2-S6) showed a significant (P1<0.001) elevation in both groups compared to levels estimated in S1 sample. Moreover, plasma cTnT levels showed a progressive increase in all patients irrespective of anesthetic regimen used reaching a peak levels in S4 sample and started to decline thereafter but still significantly higher compared to levels estimated in S1 sample. Plasma cTnT levels estimated in S2 sample showed a non-significant increase in midazolam group compared to levels estimated in isoflurane group. On contrary, plasma cTnT levels estimated in midazolam group at 16, 24, 36 and 48 hours after aortic cross-clamping were significantly higher (P<0.034, 0.01, <0.001 & =0.031, respectively) compared to levels estimated in isoflurane group. In midazolam group, there was a positive significant correlation between mechanical ventilation time and plasma cTnT levels estimated at 24-hours (r=0.413, p=0.023), respectively. However, such correlations were non-significant despite being positive in isoflurane group, (r=0.265, p>0.05).

Conclusion:
It could be concluded that the hypothesis of anesthetic myocardial protection (preconditioning and minimization of reperfusion injury) is applicable for pediatric patients with congenital heart disease who are assigned for cardiac surgery. Isoflurane-based anesthesia minimized myocardial ischemic and reperfusion injury and provided efficient cardioprotection irrespective of the type of cardiac lesion.

Key words:
Myocardial Protection, Open Heart Surgeries, Pediatric Patients, Isoflurane, Midazolam
Introduction:
Cardiopulmonary bypass and cardioplegic cardiac arrest with aortic cross-clamping are used mainly to achieve adequate exposure during various cardio-surgical procedures, but they carry a risk of local myocardial injury and systemically detrimental inflammatory effects, (Wan et al., 1996). These harmful effects may be mediated by the generation of free radicals during reperfusion, (Wu et al., 2000). Many pathophysiological processes in cardiac ischemia/reperfusion are associated with derangement of cellular ion homeostasis, with calcium overload likely having a key role in the impairment of ischemic and reperfused tissue, (Baldwin et al., 2002).

Exposing the adult myocardium to brief periods of ischemia and reperfusion induces greater tolerance to a subsequent more prolonged ischemic insult, a phenomenon known as ischemic preconditioning (IP). Ischemic preconditioning is a myocardial endogenous protection against ischemia, (Chiari et al., 2005). Ischemic stimuli cause the release of stress mediators from the heart, including adenosine, bradykinin, opioids, noradrenaline and free radicals. They contribute as initiators, which pass signals to intracellular components, such as inhibitory guanine nucleotide binding proteins (Gi proteins) and protein kinase C (PKC). Eventually, ATP-sensitive K+ channels (KATP channels) on the sarcolemma and mitochondria are activated. Mitochondrial KATP channels play a greater role than sarcolemmal KATP channels. Halogenated anesthetic agents provide protection via a mechanism similar to that of ischemic preconditioning, (Rie & Pierre, 2002). Cardioprotection by IP offers higher nitric oxide production, a lower myocardial ischemia; and better functional recovery of the hearts in coronary artery surgery patients, (Buyukates et al., 2005).

Experimental evidence has clearly demonstrated that the effects of IP are mimicked by volatile anaesthetic agents that have direct protective properties against reversible and irreversible ischemic myocardial damage, (De Hert, 2005). These properties have been related to a direct preconditioning effect but also to an effect on the extent of reperfusion injury, (Kato & Foex, 2002). Given the important role of calcium overload, some have suggested that inhaled anaesthetic preconditioning reduces ischemia/reperfusion injury by activating adenosine triphosphate-sensitive potassium channels, thereby decreasing intracellular and mitochondrial calcium in adult hearts, (Obal et al., 2005). This is often referred to as anaesthetic preconditioning; the implementation of these properties during clinical anesthesia can provide an additional tool in the prevention and/or treatment of ischemic cardiac dysfunction in the perioperative period, (Guarracino et al., 2006).

Furthermore, Chiari et al., (2005) reported that volatile halogenated anesthetics offer a myocardial protection both when administrated before a myocardial ischaemia and during reperfusion after the long ischaemia a phenomenon called postconditioning.

During repair of a congenital heart defect, the child is exposed to myocardial hypoxia. Pediatric myocardium is more sensitive to hypoxia and cardioplegic arrest than the adult. Cyanotic patients are exposed to high concentrations of oxygen when bypass starts inducing an injury similar to reperfusion injury, (Egan et al., 2005). However, the effect of inhaled anesthetic preconditioning, as well as its efficacy in intact newborn hearts, has not been addressed. Because the physiology, pharmacology, and metabolic responses of the newborn heart differ from those of the adult heart extrapolation of results from the adult heart is not necessarily warranted, (Imura et al., 2001).

Classic IP in rats is not present at birth, and the enhanced recovery of contractile function develops only at the end of the first postnatal week, (Awad et al., 1998). Baker et al., (1999) found that preconditioning can be induced in isolated perfused normoxic immature rabbit hearts. In an animal study, pregnant rats were exposed chronically to intermittent periods of hypoxia and their newborn offspring underwent periods of IP immediately after birth; neither procedure in isolation increased tolerance to subsequent periods of hypoxia, while the combination increased cardiac tolerance, (Ostadalova et al., 2002). Cheung et al., (2006), conducted a randomized controlled trial of the effects of remote IP in children undergoing repair of congenital heart defects and demonstrated the myocardial protective effects of remote IP. All patients undergoing heart surgery experience a certain amount of nonspecific myocardial injury.
documented by the release of cardiac biomarkers, (Zangrillo et al., 2005). The troponin complex consists of TnC, TnI and TnT, and its function is the regulation of striated and cardiac muscle contraction. Most intracellular cTnI and cTnT are bound to the myofibrils in the cardiac myocyte; however, a small percentage exists in a cytosolic pool (6–8% of cTnT and 3–4% of TnI), (Maynard et al., 2000). The importance of this pool is as the source of cytosolic troponins released 4–6 h after myocardial injury and continuing breakdown of the myofibrillar complex in damaged myocytes results in the prolonged elevation of the concentration of both troponins in blood, (Adamcova & Pelouch, 2001). The measurement of troponins is sensitive and specific for the detection of perioperative myocardial ischaemia. Cardiac troponin T has also been reported to be an independent predictor of early postoperative cardiovascular complications following non-cardiac surgery, (Jules-Elysee et al., 2001) as well as in that following coronary artery bypass surgery, (Holmvang et al., 2002). Elevations of blood cTnT in children were found to relate to the severity of myocardial damage and predict subsequent subclinical and clinical cardiac morbidity and mortality, (Kanaan & Chiang, 2004). This study was designed to evaluate the applicability anesthetic myocardial protection (preconditioning and minimization of reperfusion injury) using two anesthetic regimens. The plasma levels of cTnT, as a marker of myocardial ischemia was measured in pediatric patients assigned for correction of congenital heart diseases.

Patients & Methods:
This prospective, randomized, comparative study was conducted at Pediatric Cardiothoracic Anesthesia Unit, Abo El-Reish pediatric Hospital, Cairo University in conjunction with Anesthesia Department, Benha University Hospital. After obtaining approval of Ethics and Research Committee and parents consent, 60 pediatric patients were enrolled in the study through the period from Jan 2005 till October 2006. Patients with hepatic or renal dysfunction, endocrine or muscle disease were excluded. Also patients with Fallot tetralogy, if ventriculotomy is done during correction of the defect and patients with heart failure were excluded from the study. All operations were performed by the same surgeon. Patients were fasting 6 hours prior to surgery; 4 hours for breast milk and at least 2 hours for clear fluids. Preoperative intramuscular injections were avoided to prevent skeletal muscle trauma and release of troponins.

Patients were pre-medicated by oral atropine sulphate in a dose of 0.02 mg/kg and midazolam in dose of 0.5 mg/kg 30 min before induction of anesthesia. After ensuring sedation of the patients, they were transferred to the operating theatre. Noninvasive monitoring by pulse oximeter, ECG, indirect ABP, was applied. Oxygen was provided using a facemask. A peripheral venous line was inserted, then anesthesia was induced by fentanyl in dose of 3µg/kg and pancuronium bromide in a dose of 0.15 mg/kg. Manual ventilation was applied till tracheal intubation after adequate depth of Anesthesia. Then controlled mechanical ventilation was instituted using a mixture of oxygen and air to ensure normoxia and normocapnia. Arterial and central venous catheters were inserted. Monitoring of direct blood pressure, CVP, nasopharyngeal and peripheral temperature, urine output was conducted. Adequate depth of anesthesia was ensured using BIS considering a level of 40-60 was adequate.

Patients were randomly categorized into 2 equal groups (n=30) according to the type of anesthetic used for maintenance: Midazolam group received a continuous infusion of midazolam 0.2 mg/kg/hour and isoflurane group maintained by an end-tidal concentration of isoflurane of 1-1.5%throughout the operation. If considerable hypotension exceeding 20% of the patient base line titration of the inhaled anesthetic to maintain adequate arterial blood pressure if the possible causes were corrected. Each patient received a continuous infusion of fentanyl at rate of 2-3 µg/kg/hr throughout the duration of surgery. Additional doses were given when necessary during skin incision, sternotomy, pericardium opening and aortic cannulation. Activated clotting time (ACT) and arterial blood gases were estimated after induction of anesthesia and heparin was administered in a dose of 4 mg/kg so as to keep ACT value >480 seconds before institution of CPB. Cardiopulmonary bypass was instituted with a Dideco hollow fibre oxygenator with a blood flow between 200 and 300 ml/kg/min. The priming
volume is calculated according to the patient’s weight, containing Ringer’s solution, albumin, mannitol, blood, and heparin. Cooling down during bypass to temperature of 28°C was performed. Hemodynamic monitoring and recording of HR, CVP and systolic (SAP) and diastolic (DAP) and mean arterial blood pressures (MAP). Cardioplegia was prepared from blood and crystalloid in a ratio of 1:1 mixture at 4°C. The concentration of the components of cardioplegia was: K⁺ 30 mmol/l, NaHCO₃ 24 mmol/l, Mg²⁺ is 15 mmol/l and lidocaine HCl 120 mg/l. The first dose is 20 ml/kg followed by subsequent doses of 10 ml/kg every 20-30 minutes or with return of electrical activity. Patients underwent modified ultrafiltration at the end of the bypass. Ischemic time, defined as the time elapsed since aortic clamping till aortic declamping, duration of bypass and total duration of surgery were recorded. Need for defibrillation and its frequency was also recorded.

Six blood samples (0.5 ml) were taken immediately after induction of anesthesia (S1), 8-hours (S2), 16-hours (S3), 24-hours (S4), 36-hours (S5) and 48-hours (S6) after aortic clamping. Samples were collected in a Gel-Microtainer tube and immediately analyzed by the hospital laboratory using the Elecsys Modular E170 immunochemistry analyzer (Cardiac Troponin T, Roche Diagnostics, Mannheim) for estimation of plasma cardiac troponin T (cTnT).

Arterial oxygen tension, pH, base excess, bicarbonate, and lactate were measured immediately after admission to PICU and at any time if the patient condition required. Ventilator hours and the need for inotropic support and their doses and duration were recorded. Fluid intake (including crystalloids, colloids, and blood products), output (urine, blood, serous fluid loss and chest drain), and fluid balance were recorded hourly over a 36-h period following admission to PICU.

**Statistical analysis:**

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Z-test for unrelated samples and Chi-square (X²) test. Possible relationships were investigated using Pearson linear regression. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

**Results:**

The study included 60 patients; 36 males and 24 females 3-29 months old (mean 14.4±7) and body weight of 3.5-10.1 Kg (mean 7±1.2). There was a non-significant (p>0.05) difference between groups as regards age, sex and weight of enrolled patients, (Table 1). Surgical procedures performed were presented in table (2) showed a non-significant (p>0.05) difference between the two groups as regards patients’ distribution according to surgical procedure performed.

There was a non-significant (p>0.05) difference between the studied groups as regards surgery, bypass or clamping times. During the stay in PICU, the mean duration of mechanical ventilation showed a non-significant (p>0.05) difference between the studied groups, (Table 3). Plasma cTnT levels estimated after aortic cross-clamping (S2-S6) showed a significant (P<0.001) elevation in both groups compared to levels estimated immediately after induction of anesthesia (S1). Moreover, plasma cTnT levels showed a progressive increase in all patients irrespective of anesthetic regimen used reaching a peak levels at 24-hours after aortic cross-clamping (S4) and started to decline thereafter but still significantly higher compared to levels estimated immediately after induction of anesthesia. Plasma cTnT levels estimated 8-hrs after aortic cross-clamping (S2) showed a non-significant increase in midazolam group compared to levels estimated in isoflurane group. On contrary, plasma cTnT levels estimated in midazolam group at 16, 24, 36 and 48 hours after aortic cross-clamping were significantly higher (P<0.034, 0.01, <0.001 & =0.031, respectively) compared to levels estimated in isoflurane groups, (Table 4, Fig. 1).

In midazolam group, there was a positive significant correlation between mechanical ventilation time and plasma cTnT levels estimated at 24-hours after clamping (r=0.413, p=0.023), respectively, (Fig. 2a). However, such correlations were non-significant despite being positive in isoflurane group, (r=0.265, p>0.05), respectively, (Fig. 2b).

There were no significant differences in arterial oxygen tension, pH, base excess, bicarbonate, or lactate between the groups. The differences in hemodynamic variable, fluid balance, ratios and duration of mechanical ventilation in the 36 hours following admission to the PICU were not
significantly (p>0.05) different between both groups. Moreover, there were no differences between the groups in the use of inotropic drugs on admission to the intensive care or 24 h later.

Discussion:
There was a significant increase of plasma cTnT in all samples examined after aortic cross-clamping (S2-S6), with a progressive increase in all patients irrespective of anesthetic regimen used reaching a peak levels at 24-hours after aortic cross-clamping (S4). This rise started to decline thereafter but still significantly higher compared to levels estimated immediately after induction of anesthesia (S1). This result illustrates the effect of ischemia resulting from aortic cross clamping on the myocardium and hence the production of ischemia markers. These data agreed with previous studies reporting increased plasma levels of cardiac troponins after cardiac surgery; Immer et al., (1999), reported that cardiac troponin serum levels after open heart surgery in children and infants 4 h after admission to the ICU allowed anticipation of the postoperative course and correlated with the incidence of significant postoperative complications. Zhang et al., (2000) found that the elevation of troponin T is closely related to cardiopulmonary bypass, especially the duration of aortic cross clamping, insufficiency of cardioplegia, and metabolic acidosis. Moreover, Chechlia et al., (2003) and Cheung et al., (2006) reported significant increases of cTnT in children undergoing repair of congenital heart defects especially in samples obtained immediately after release of aortic clamping. Also, Malagon et al., (2005) reported significant increases of plasma cTnT after cardiac surgery in pediatric patients in all samples taken at 8, 15 and 24 hours after admission to PICU.

Plasma cTnT levels at (S2) despite were significantly higher compared to (S1) and lower in isoflurane group than in midazolam group but the difference between groups was not significant. These data point to the applicability of isoflurane for preconditioning and agreed with Belhomme et al., (1999), who found that isoflurane preconditioning significantly reduced the release of cardiac troponins and concluded that the obtained data support a cardioprotective effect of isoflurane and, more generally, demonstrate the feasibility of pharmacologically preconditioning the human heart during cardiac surgery. Similarly, Haroun-Bizri et al., (2001), reported that administration of isoflurane before aortic cross-clamping in patients undergoing coronary artery bypass graft surgery may optimize the myocardial protective effect of cardioplegia and may be particularly advantageous whenever prolonged periods of aortic cross-clamping or inadequate delivery of cardioplegia is expected. On contrary, Wang et al., (2004), compared isoflurane preconditioning versus non-conditioned patients and found isoflurane patients released slightly less creatine kinase cardiac isoenzyme (CK-MB) and troponin than the controls postoperatively, but the difference was not significant. However, results obtained by Lee et al., (2006), support the preconditioning effect of isoflurane in patients undergoing coronary artery bypass graft surgery as clinically feasible and providing optimal cardiac protection.

On the other hand, plasma cTnT levels estimated in patients received midazolam in (S3), (S4), (S5), and (S6) were significantly higher (P<0.034, 0.01, <0.001 & =0.031, respectively) compared to levels estimated in patients received by isoflurane. Furthermore, isoflurane cardioprotective effect extended after release of aortic clamp till 24-hours after clamping manifested as shorter duration of postoperative mechanical ventilation with a positive non-significant correlation between mechanical ventilation and aortic cross clamping with a positive non-significant correlation between mechanical ventilation and total intravenous and inhalational anesthetics; De Hert et al., (2004), found the use of inhalational anesthetics resulted in lower postoperative troponin concentrations and lower need for prolonged inotropic support with a shorter ICU and length of hospital stay and attributed this to a better preservation of early postoperative myocardial function. Also, Guarracino et al., (2006), compared cardiac troponin release in patients receiving either volatile anesthetics or total intravenous anesthesia for cardiac surgery on the beating heart and found myocardial damage measured by cardiac troponin release, could be reduced by volatile anesthetics. Moreover, Xia et al., (2006), evaluated the cardioprotective effect of
isoflurane compared to small and large dose propofol and found the cardioprotective effect of propofol is dose-dependent and only higher dose propofol is advantageous compared to isoflurane. The significant reduction of plasma cTnT levels estimated in 53-56 samples in isoflurane group compared to midazolam group that extended for 48 hours after time of aortic clamping illustrated the beneficial cardioprotection effect of isoflurane and could be attributed to the ability of isoflurane to combat the injurious effects of ischemia and reperfusion after aortic decalmping. Various experimental studies tried to investigate the metabolic pathway of myocardial preconditioning effect of isoflurane; Raphael et al., (2005) and Krolikowski et al., (2006), reported that administration of isoflurane during early reperfusion after prolonged coronary artery occlusion decreases myocardial infarct size by activating phosphatidylinositol-3-kinase (PI3K) signal transduction and the extracellular signal-related kinases represent a redundant mechanism by which signaling elements downstream from PI3K, including 70-kDa ribosomal protein S6 kinase and endothelial nitric oxide synthase may be activated to reduce reperfusion injury. Krolikowski et al., (2005), found inhibition of the mitochondrial permeability transition pore (mPTP) enhances, whereas opening abolishes isoflurane-induced postconditioning and isoflurane-induced inhibition of mitochondrial permeability transition is dependent on activation of mitochondrial KATP channels in vivo. Wang et al., (2006), suggested that enhanced expression of the antiapoptotic protein B cell lymphoma-2 (Bcl-2) mediates isoflurane-induced postconditioning by indirectly modulating the mPTP activity in vivo. Pagel et al., (2006), reported that glycogen synthase kinase (GSK)-beta inhibition enhances isoflurane-induced protection against infarction during early reperfusion via an mPTP-dependent mechanism. Feng et al., (2006), reported that isoflurane postconditioning retains its marked protection in diseased myocardium and the infarct-remodeled myocardium is receptive to protection by isoflurane postconditioning via protein kinase B/Akt signaling. Kalenka et al., (2006), evaluated post-anesthetic myocardial protein expression profiles associated with the anesthesia with isoflurane, sevoflurane or desflurane and found that these volatile anesthetics promote a distinct change in the myocardial protein expression profile, whereby changes in the expression pattern still exist 72 h after anesthesia and these changes are closely related to cardioprotection. Tessier-Vetzel et al., (2006), found that isoflurane potentiates postconditioning at reperfusion through a NO-dependent mechanism. Bains et al., (2006), reported that isoflurane and sevoflurane may act as metabolic inhibitors by depolarizing pre-synaptic mitochondria through inhibition of the electron transport chain, although isoflurane seems to inhibit mitochondrial function more significantly than sevoflurane and both agents inhibit the respiratory chain sufficiently to cause ATP synthase reversal.

It could be concluded that the hypothesis of anesthetic myocardial protection is applicable for pediatric patients with congenital heart disease who are assigned for cardiac surgery. Isoflurane-based anesthesia minimized myocardial ischemic and ischemia-reperfusion injury and provided efficient cardioprotection irrespective of the type of cardiac lesion, duration aortic cross clamping.

References:


Table (1): Patients’ distribution according to their demographic data

<table>
<thead>
<tr>
<th>Data</th>
<th>Midazolam group</th>
<th>Isoflurane group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>14±7.8 (3-24)</td>
<td>14±7.4 (6-29)</td>
<td>14±7</td>
</tr>
<tr>
<td>Sex; M:F</td>
<td>20:10</td>
<td>16:14</td>
<td>36:24</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>7±1.3 (3.5-9.8)</td>
<td>6.9±1.1 (3.8-10.1)</td>
<td>7±1.2</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD, ratios and numbers; ranges are in parenthesis

Table (2): Patients’ distribution according to surgical procedures performed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Midazolam group</th>
<th>Isoflurane group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>15 (50%)</td>
<td>16 (53.4%)</td>
<td>31</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>5 (16.7%)</td>
<td>5 (20%)</td>
<td>11</td>
</tr>
<tr>
<td>Arterial switch</td>
<td>4 (13.3%)</td>
<td>2 (6.6%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Partial Atrioventricular canal defect</td>
<td>4 (13.3%)</td>
<td>5 (16.7%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous drainage</td>
<td>2 (6.7%)</td>
<td>1 (3.3%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
</tbody>
</table>

Data are presented as numbers; percentages are in parenthesis

Table (3): Operative & PICU data of studied patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Midazolam group</th>
<th>Isoflurane group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic time (min)</td>
<td>56.7±35.5 (20-155)</td>
<td>46.7±30 (20-145)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>116.3±14 (90-140)</td>
<td>119.2±12.4 (95-140)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>186±21.1 (150-210)</td>
<td>193±13.5 (165-210)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (hours)</td>
<td>11.7±11.3 (4-45)</td>
<td>9.9±10.3 (4-44)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD and numbers; ranges are in parenthesis
Table (4): Plasma cTnT (ng/ml) levels estimated in the studied groups

<table>
<thead>
<tr>
<th>Group</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Midazolam group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD (range)</td>
<td>0.65±0.1</td>
<td>2±0.22</td>
<td>2.25±0.32</td>
<td>2.67±0.5</td>
<td>2.38±0.31</td>
<td>2.08±0.22</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Isoflurane group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD (range)</td>
<td>0.67±0.1</td>
<td>1.93±0.29</td>
<td>2.06±0.28</td>
<td>2.39±0.45</td>
<td>2.01±0.25</td>
<td>1.94±0.26</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P_1: significance of difference compared to S1 value
P_2: significance of difference compared to S2 value
P_3: significance of difference compared to S3 value
P_4: significance of difference compared to S4 value
P_5: significance of difference compared to S5 value
P_6: significance of difference compared to Ketamine group
Fig. (2): Correlation between mechanical ventilation time and plasma cTnT levels estimated at 24-hours after aortic cross-clamping in both groups