

# The effect of sevoflurane induction on the myocardial performance index in healthy individuals

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**Background:** The myocardial performance (Tei) index is a simple, reproducible and easily performed measure of cardiac performance. Its ease of use and proven clinical application make this an attractive measure perioperatively. For appropriate use of this index under sevoflurane anaesthesia, drug effects on normal values need to be defined.

**Methods:** A total of 38 ASA 1 patients were consecutively included in this study. Induction was by sevoflurane inhalation. Steady state was defined as 3–5 min spontaneous tidal ventilation with an end-tidal sevoflurane concentration of at least 2.3%. Baseline and steady-state measurements included haemodynamics and four-chamber transthoracic echocardiographic image acquisition. Offline analysis focused on tissue Doppler studies of the lateral mitral annulus. Discrete variables before and after induction were compared.

**Results:** Changes in simple haemodynamic variables were as expected (Systolic blood pressure: mean [95% CI] –11.62 [–15.96 to –7.27]; diastolic blood pressure: mean [95% CI] –6.46 [–11.65 to –1.28]; heart rate: mean [95% CI] 2.66 [–1.72 to 7.05]). Isovolumic contraction time decreased from baseline (mean [95% CI] –3.37 [–5.11 to –1.64]). Isovolumic relaxation time also decreased (mean [95% CI] –7.44 [–10.23 to –4.66]). Ejection time decreased (mean [95% CI] –4.41 [–11.62 to 2.80]). This saw a consistent decrease in the Tei index with a p-value of < 0.0001 (mean [95% CI] –0.035 [–0.050 to –0.021]).

**Conclusion:** Sevoflurane at 1-MAC minimally decreases the Tei index. This implies that, overall, myocardial mechanics/performance in healthy individuals is not negatively affected by sevoflurane anaesthesia. Reference values for this index appear to be applicable for patients under sevoflurane anaesthesia.

**Keywords:** Anaesthetics volatile, sevoflurane, heart, myocardial function, Tei index, tissue Doppler echocardiography

## Introduction

Echocardiography has become indispensable in the perioperative setting.<sup>1</sup> The Myocardial Performance (Tei) index offers a reliable measure of overall cardiac function in normal and pathological states.<sup>2–5</sup> It is said to be independent of both haemodynamic and loading alterations<sup>2,3,6–9</sup> although this is frequently questioned.<sup>10</sup> Nevertheless, it could be an attractive perioperative gauge as it is perceived as relatively easy to measure and is reproducible in a number of clinical situations.<sup>5</sup>

The Tei index incorporates systolic and diastolic function into a single numeric value and correlates well with conventional haemodynamic measures of these,<sup>11,12</sup> with some suggestion that it may be superior.<sup>13,14</sup> It is a time interval index conventionally derived using pulsed-wave Doppler interrogation of trans-mitral inflow and left ventricular outflow using the equation  $Tei = (IVCT+IVRT)/ET$ , where IVCT is the isovolumic contraction time and IVRT is the isovolumic relaxation time.<sup>2</sup> A tissue Doppler imaging (TDI) derived alternative has the added benefit of single cardiac cycle interrogation and correlates well with the conventional method (Figure 1).<sup>15,16</sup> The mean normal value of the Tei index for the left ventricle is  $0.39 \pm 0.05$ .<sup>2</sup>

There is evidence to suggest that acute changes to preload alter the Tei index.<sup>5,10,17–19</sup> This may purely be a normal physiological response to preload changes which the index is tracking, and could prove useful when evaluating preload optimisation *in vivo*.<sup>9</sup> The debate over the clinical usefulness of the Tei index is largely centred on this contradiction.<sup>10</sup>

Sevoflurane is widely used, is relatively cardiac stable and appears to offer pharmacological preconditioning.<sup>19–23</sup> It is

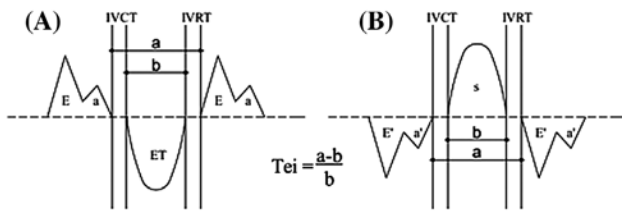
thought to be negatively inotropic through its effects on calcium homeostasis, but at clinically relevant doses this does not appear to affect simple haemodynamics.<sup>20</sup> It has been shown to improve diastolic dysfunction.<sup>23–26</sup> The effect of sevoflurane on the Tei index has not yet been studied. There is global consensus that echocardiographic parameters may need to be redefined for the anaesthetised patient.<sup>27</sup>

This study tested the null hypothesis that sevoflurane, administered at clinically relevant doses, does not affect overall cardiac function when assessed using the Tei index. This was tested in spontaneously breathing healthy individuals. As a secondary outcome, applicability of normal Tei index values under sevoflurane anaesthesia was explored.

## Methods

This study was approved by the Ethics Committee of the Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa (ECUFS NR 55/2013). Institutional approval was obtained to consecutively enrol male and female American Society of Anesthesiologists (ASA) 1 patients scheduled for elective surgery at the local Academic Hospital. All participants gave written, informed consent.

Inclusion criteria were: age 18–50 years; ASA 1 status; effort tolerance > 4 METS (metabolic equivalents of task) as assessed with the Duke activity index; and a normal preoperative cardiopulmonary clinical examination. Exclusion criteria comprised: any need for haemodynamic support or positive pressure airway manoeuvres for airway obstruction; any need for mechanical ventilatory support; abnormal baseline Tei index; pregnancy; and intellectual disability. Patients were all examined



**Figure 1:** (A) The original Doppler-derived Tei index showing the E and a waves of transmitral inflow, ejection time (ET) as measured in the left ventricular outflow tract. Isovolumic contraction (IVCT) and relaxation (IVRT) times are indicated. (B) The tissue Doppler derived alternative showing the E', a' and s waves typical of lateral mitral annular motion. Again the isovolumic contraction and relaxation times are shown.

by the principal investigator (ACK) and no pre-medication was prescribed. Patients were allowed to opt for pre-medication and if they chose this they were excluded from the study.

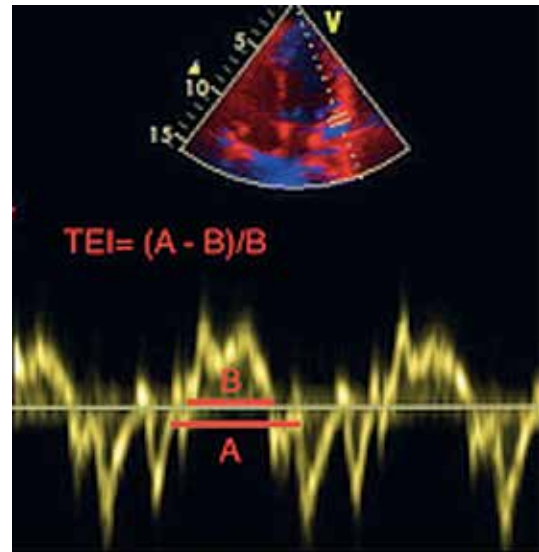
On arrival in theatre intravenous access was secured and baseline pulse oximetry, three-lead electrocardiogram and non-invasive blood pressure were recorded (Datex-Ohmeda, GE, Helsinki, Finland). Baseline echocardiographic images were captured before induction.

Patients received an inhalational induction using sevoflurane (Sojourn™, Safeline Pharmaceuticals (Pty) Ltd) at 4–6% in 40% oxygen and air. Airway support consisted of chin-lift and jaw-thrust manoeuvres only. Supraglottic airway device (SGA) placement was performed when the steady-state concentration of sevoflurane was achieved. Steady-state concentration was defined as an end-tidal sevoflurane concentration of 2.3% for 3–5 min with spontaneous tidal volume breathing. Spontaneous breathing with no mechanical assistance was maintained throughout. Once the SGA was placed, all haemodynamic and echocardiographic measurements were repeated. The duration of the steady-state assessment was minimised and end tidal carbon dioxide, measured using standard side stream capnography, did not increase above 45 mmHg before conclusion. No other drugs were administered. At the end of data collection the anaesthetic and surgery proceeded as planned by the attending team.

All echocardiographic assessments were made using a Vivid S6 (General Electric Healthcare Systems, Helsinki, Finland) sonographic workstation. A transthoracic protocol was followed using a 3.6–1.5 MHz cardiac probe with simultaneous ECG monitoring. Using the standard apical four-chamber view, tissue Doppler imaging (TDI) of the lateral mitral annulus was performed. Patients were kept in an identical supine position pre- and post-induction.

Comprehensive off-line echocardiographic analysis allowed us to measure the isovolumic contraction time (IVCT), the isovolumic relaxation time (IVRT) and the ejection time (ET). The s'-wave duration was used as a surrogate for ET.<sup>15,16</sup> The duration between the end of the a'-wave and the following E'-wave was also recorded, as well as the E' velocity. (Figure 2). The Tei index was derived using the alternative TDI-derived method described earlier.<sup>15,16</sup>

Continuous variables were presented as mean values and standard deviations. Differences between pre- and post-induction variables were reported as 95% confidence intervals. The paired t-test was applied and differences with a *p*-value of < 0.05 were regarded as statistically significant. All statistical



**Notes:** A represents the duration from the a' wave to the subsequent E' wave, with B representing the S wave duration, used as a surrogate of the ejection time.

**Figure 2:** Tissue Doppler imaging of the lateral mitral annulus.

analysis was done by the Department of Biostatistics, University of the Free State, Bloemfontein, South Africa using the SAS® 9.3 software package (SAS Institute, Cary, IN, USA).

## Results

Thirty-eight patients were enrolled, with the first two acting as a demonstration of the imaging protocol to be used. They were excluded from the final data-set. Further exclusions are outlined in Figure 3. The patients excluded for airway obstruction relate to patients who required any positive pressure airway intervention during induction but before steady state was achieved, at which time an SGA device would be placed. Three patients had abnormal Tei-index measurements at baseline and were excluded from the trial as this study aimed to investigate only normal hearts. The final data-set consisted of 27 patients. Demographic data are summarised in Table 1. Haemodynamic and echocardiographic findings are summarised in Table 2.

## Discussion

The current study attempted to define the effect of sevoflurane on the Tei index. As a secondary outcome we examined whether accepted normal values are potentially applicable under sevoflurane anaesthesia. Patients were healthy and expected to maintain basic cardiopulmonary homeostasis as gauged by haemodynamic measures, capnography and oxygen saturation. Any intervention in this regard resulted in exclusion. No other drugs were administered and only sevoflurane was used to induce anaesthesia. Once data collection was complete, the attending anaesthetist continued with his/her planned anaesthetic technique. It was felt that, in terms of the application of the Tei index, this population was a representative sample.

This study showed a consistent decrease in the Tei index calculated using the TDI method.<sup>15,16</sup> The mean Tei index value at baseline was normal for patients included in this study (0.40) and had a narrow confidence interval. When considering the ways in which sevoflurane could influence the Tei index, it is best to consider each of the components that make up the index separately. These are described by the original formula for calculating the Tei index:  $TEI = (IVCT + IVRT) / ET$ .<sup>2,3</sup>

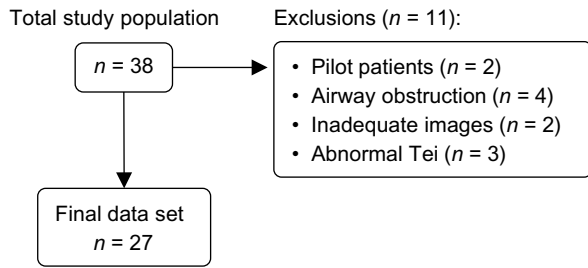


Figure 3: Study population.

Table 1: Demographic data

Item	Data	
Age (mean)	31	
Gender	Male	26% (n = 7)
	Female	74% (n = 20)
Ethnicity	White	22% (n = 6)
	Black	74% (n = 20)
	Other	4% (n = 1)

Table 2: Pre- and post-induction variables

	Baseline (mean; SD)	Steady state (mean; SD)	Difference (mean; 95% CI; p-value)
Heart rate (bpm)	79; 11.82	81; 13.63	2.67; -1.72 to 7.06; 0.223
SBP (mmHg)	124; 15.61	112; 16.50	-11.62; -15.96 to -7.27; < 0.0001
DBP (mmHg)	73; 11.02	67; 11.49	-6.46; -11.65 to -1.28; 0.017
IVCT (ms)	39.26; 6.04	35.89; 6.36	-3.37; -5.11 to -1.64; 0.0005
IVRT (ms)	65.04; 10.17	57.59; 9.26	-7.44; -10.23 to -4.66; < 0.0001
s'-wave duration (ms)	282.37; 25.48	277.96; 20.58	-4.41; -11.62 to 2.8; 0.22
E'-velocity (cm.s <sup>-1</sup> )	15.21; 2.60	15.04; 2.66	-0.17; -0.98 to 0.64; 0.671
Tei index	0.40; 0.02	0.36; 0.04	-0.04; -0.05 to -0.02; < 0.0001

Notes: bpm = beats per minute; SBP (mmHg) = systolic blood pressure in millimetres of mercury; DBP (mmHg) = diastolic blood pressure in millimetres of mercury; IVCT (ms) = isovolumic contraction time in milliseconds; IVRT (ms) = isovolumic relaxation time in milliseconds; s'-wave duration (ms) = ejection time in milliseconds; E'-velocity in centimetres per second.

Isovolumic contraction time (IVCT) is defined as the period between atrioventricular (AV) valve closure and ventriculoarterial (VA) valve opening.<sup>28</sup> This study demonstrated a statistically significant decrement of the IVCT (-3.37; p-value 0.0005). Isovolumic relaxation time (IVRT) is defined as the period between VA-valve closure and AV-valve opening.<sup>28</sup> The reduction in the IVRT was also significant in this study (-7.44, p-value < 0.0001) and this correlates well with previous work studying patients under anaesthesia, breathing spontaneously.<sup>23,25,27</sup> The mechanisms for the changes observed could potentially be due to the effects sevoflurane has on conductive tissue and therefore electromechanical coupling.<sup>29-33</sup> Sevoflurane's effects on conduction and contractility are traditionally thought to be negative, and would therefore be expected to prolong time-interval indices. The fact that this study showed shorter

isovolumic times suggests that it is more likely explained by haemodynamic changes across the valves.

Delayed mitral valve closure and/or expedited aortic valve opening would explain the shorter IVCT. Mitral valve closure occurs when left atrial pressure (LAP) is surpassed by left ventricular pressure.<sup>28</sup> Conventionally, left atrial pressure is expected to be lowered by sevoflurane due to the drug's effect on atrial preload.<sup>20</sup> Recent echocardiographic evidence shows minimal changes to left atrial reservoir function during sevoflurane anaesthesia while breathing spontaneously,<sup>34</sup> suggesting minimal changes to LAP in this setting. Previous work has shown that late ventricular filling may be slightly impaired, indicating a negative inotropic effect on atrial systole.<sup>23,24,26</sup> This could potentially translate into a higher than expected LAP at end diastole, causing delayed mitral valve closure. Sevoflurane has been shown to negatively influence dP/dT(max) during systole, implying a negative inotropic effect.<sup>33</sup> Recent echocardiographic evidence in patients under sevoflurane anaesthesia, using clinically relevant doses, points to the contrary.<sup>23,25</sup> A smaller than expected effect on the inotropic state of the left ventricle, coupled with a lowered aortic diastolic blood pressure, would explain earlier aortic valve opening. The change in IVCT illustrated by this study is likely due to a combination of factors, which appear to include loading changes across the valves. This brings the load independency of the Tei index into question again.<sup>5</sup>

Delayed closure of the aortic valve and/or earlier opening of the mitral valve will shorten the IVRT. Sevoflurane is known to decrease systemic vascular resistance (SVR) in a dose-dependent manner.<sup>20</sup> This could cause a greater pressure discrepancy between the left ventricle and the aorta during early diastole, delaying aortic valve closure. Improved early diastolic function has been suggested under sevoflurane anaesthesia.<sup>23,26</sup> Various potential explanations have been offered and it is thought that altered myocardial calcium homeostasis is likely to be implicated.<sup>23,26</sup> There is, however, conflicting evidence. Specifically, previous work by Bolliger *et al.* has shown a consistent decrease in the E' velocity under sevoflurane anaesthesia in healthy individuals during spontaneous respiration.<sup>25</sup> This echocardiographic measure of diastolic function correlates well with the rate of relaxation (-dP/dT), also known as Tau.<sup>25,35</sup> The present study showed a slight decrease in E' velocity, which was not statistically significant (-0.17, p-value = 0.671). An enhanced rate of relaxation would explain earlier ventricular and atrial pressure approximation during diastole, resulting in expedited mitral valve opening. The change in loading conditions across the mitral and aortic valves, therefore, appears to be the likely cause for the reduction in the IVRT illustrated in this study.

The duration of the s'-wave was accepted as a surrogate for the ejection time (ET) during this study.<sup>15,16</sup> The study shows a minor decrease with poor clinical and statistical significance (-4.41, p-value = 0.22). Seminal work on the determinants of the ET revealed that heart rate was the major determinant of the period, with stroke index and loading conditions playing relatively minor roles.<sup>36</sup> The heart rate findings in the present study showed a minor difference which was not significant (2.67, p-value = 0.223). This study showed a consistent decrease in the duration between the a'-wave and the E'-wave which is statistically significant (-17.37, p-value = 0.0024). It is this difference, an important part of the numerator for the Tei index ratio,<sup>2,3,15,16</sup> which appears to explain the overall change in the index. This finding also

underlines the important part changes to the IVCT and IVRT have to play in affecting the Tei index under sevoflurane anaesthesia.

The incidental finding that our study population had IVCT and IVRT values that differed slightly from accepted normal values cannot be explained by this study. These differences are very small, especially when considering that normal IVCT is 30 ms and IVRT  $70 \pm 12$  ms. Our data show time indices that overlap with values accepted as normal. The mean Tei index value was normal. This implies that the ratio of the various time indices remained normal for our population. Correlations between time indices and race, age and physical status could be grounds for further research and will not be discussed here.

The final consideration should be how sevoflurane affects the 'neurohormonal loading conditions' of the myocardium. Circulating catecholamines have a directly positive inotropic and lusitropic effect.<sup>28</sup> Sevoflurane used for rapid induction of general anaesthesia has been shown to decrease blood pressure and adrenaline levels but increase noradrenaline levels.<sup>37,38</sup> This is similar to what is seen during maintenance of anaesthesia after rapid dose increases of sevoflurane.<sup>39</sup> Sevoflurane therefore appears to attenuate the sympathetic response to a reduced SVR, responding only with an increase in circulating noradrenaline. Noradrenaline affects the myocardium directly, but this effect is likely not significant when compared with adrenaline.<sup>28</sup> Neurohormonal responses to sevoflurane are, therefore, less likely to explain the changes seen to the IVCT and IVRT.

The manner in which clinical doses of sevoflurane affect the Tei index in healthy individuals is likely of negligible clinical relevance, but is statistically significant ( $-0.03$ ,  $p$ -value  $< 0.0001$ ). The change observed in the Tei index would imply that overall cardiac function is not negatively influenced by clinically useful doses of sevoflurane in this population, when breathing spontaneously. This study lacks the power that a large epidemiological study would have had on stating whether the accepted normal values are applicable under anaesthesia, but the statistical significance of the finding allows us to make the supposition that they are. The load independency of the index is, however, again brought into question. Further research, investigating the effects of sevoflurane on this index in patients with cardiovascular disease, could deepen our understanding of how the drug interferes with cardiovascular mechanics with a compromised substrate. The effects of other anaesthetic drugs and intermittent positive pressure ventilation need to be investigated to make these findings clinically applicable. It is hoped that this study will serve as a useful reference point.

The Tei index remains an attractive, easy to use perioperative measure and the relatively small changes to the value caused by sevoflurane should encourage its application.

### Study limitations

The present study population is small but compares well with previous work using a similar study design examining similar echocardiographic parameters.<sup>23,25,26</sup> For this reason a power analysis was excluded. Demographic data reveal a study population skewed towards black African females. The Tei index has an apparent universal application<sup>2</sup> so this observation should not affect the quality of the data. Echocardiographic investigations were performed by a novice echocardiographer (ACK). In an attempt to overcome investigation bias, an experienced cardiothoracic anaesthetist (JvdW) reviewed image quality and measurements randomly. Where unexpected

measurements were encountered these scans were all reviewed. Studies not fit for accurate assessment were excluded from the final data-set. The principal investigator was responsible for data analysis and this was therefore not blinded, which is another potential source of bias. An effort to minimise this was made by random review of technique by an experienced echocardiographer (JvdW).

### Author contributions

ACK: data collection, literature review and writing of the manuscript. JvdW: reviewing of data, editing of the manuscript. EWT: editing of the manuscript.

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