THE EFFECT OF SEDATION ON HEART RATE VARIABILITY DURING TRANSESOPHAGEAL ECHOCARDIOGRAPHY: A COMPARISON OF HYPNOTIC SEDATION WITH MEDICAL SEDATION

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ABSTRACT

Background: There is no ideal sedation technique that can be used during Transesophageal Echocardiography (TEE) and the data concerning the effects of available sedation techniques on Heart rate variability (HRV) are limited. Our study aimed at comparing the effects of sedation through hypnotherapy with medical sedation achieved by midazolam on HRV.

Methods: We recruited 76 patients with an indication of TEE; the age range was 18-83 years. The patients were randomized into 3 groups. In Group Topical (Group T), 26 patients who underwent the procedure under topical pharyngeal anesthesia; in Group Midazolam (Group D), 23 patients received midazolam; and in Group Hypnosis (Group H), 27 patients received hypnosis. All patients had an IV port. Throughout the procedure, heart rate, electrocardiography (ECG) rhythm, and peripheral O2 saturation were monitored with a non-invasive monitor, and blood pressure measurements were taken every 3 minutes. Holter rhythm recordings were obtained from all patients during procedure.

Results: When time domain parameters for HRV were compared in all three groups, the hypnosis group demonstrated a significant increase in both the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50) (Group H p:0.001, Group T p:0.002) and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) compared to Groups D and T (Group H p:0.001, Group T p:0.04). With regard to frequency domain parameters, in the hypnosis group, the low-frequency (LF) was decreased, and although the high-frequency (HF) was increased, this difference was not at the level of statistical significance (p:0.12, p:0.72, respectively). However, the LF/HF decreases were statistically significant (Groups D p:0.001 and T p:0.001) when compared with the midazolam group.

Conclusion: Contrary to sedation with midazolam, when hypnosis is used for sedation in
TEE patients, the autonomic cardiac tone is modified to a significant extent. Hypnotic sedation achieves this by increasing the parasympathetic activity, decreasing the sympathetic activity and altering the sympathovagal interaction balance.

**Keywords:** transesophageal echocardiography, heart rate variability, hypnotic sedation, midazolam

**Introduction:**

Transesophageal Echocardiography (TEE) is a diagnostic test utilized in patients with cardiovascular problems when conventional Transthoracic Echocardiography (TTE) does not yield sufficient information. Unlike TTE, TEE is an invasive diagnostic tool that hinders the comfort of the patient and causes nausea, a gag reflex, dyspnea and emotional distress. Generally, TEE is performed in cardiology departments under topical anesthesia. Most patients cannot tolerate the introduction of the probe under topical anesthesia, and they feel ill during the procedure. Because topical anesthesia cannot totally eliminate the gag reflex, a more effective and deeper sedation might be necessary for those patients who cannot tolerate the procedure [1,2]. Before pharyngeal intubation, for medical sedation purposes, sedation studies were performed with a mild and short acting sedative and anxiolytic by using midazolam, which is a benzodiazepine. Propofol vs. midazolam and midazolam vs. remifentanyl were compared to see mild and deep sedation [3-5]. Hypnotic sedation has been shown to decrease the length of the postoperative stay, use of analgesics, pain and anxiety, and nausea and vomiting in breast biopsies, general surgery, open heart surgery and plastic surgery[6-11].

Hypnotic sedation can also decrease the frequency of pain during the treatment for non-cardiac chest pain and can decrease cardiac sympathetic activity during a percutaneous transluminal coronary angioplasty. [12-13]
A heart rate variability (HRV) analysis evaluates the condition of the autonomic nervous system, which is responsible for regulating cardiac activity and cardiac health in general. Thus, HRV is used to evaluate both the sympathetic and parasympathetic modulation of the heart rate [14]. There are a limited number of studies on HRV during TEE procedures that have been performed under both medical and hypnotic sedation. The aim of our study was to determine the effects of sedation with midazolam and hypnotherapy on HRV.

MATERIAL AND METHODS:

Patients:

Seventy-six patients (37 male and 39 female) between 18-83 years of age who were indicated for TEE as confirmed by our Cardiology Unit during October-December 2010 were included in our study. Patients below 18 years of age; those with heart failure, ventricular arrhythmias, complex congenital heart conditions, and obstructive lung diseases; those who cannot tolerate TEE, those who use benzodiazepines, antidepressants and antipsychotics or medications influencing the heart rate; and those with thyroid conditions were excluded from the study.

All of the patients who agreed to participate in the study signed informed consent forms, and the approval of the hospital ethics committee was obtained. The patients were randomized into 3 groups. Group Topical (Group T) had 26 patients who received only topical anesthesia with 1% lidocaine; Group Midazolam (Group D) included 23 patients who received midazolam and Group Hypnosis (Group H) included 27 patients who underwent hypnosis. All of the patients were in sinus rhythm. Before the procedure, IV access was established. Patients were monitored with a non-invasive monitor throughout the procedure for heart rate, ECG rhythm and O₂ saturation. Blood pressure measurements were taken from the right arm.
every 3-5 minutes. The monitoring of these parameters began before the patient swallowed
the TEE probe and was concluded after the probe was retrieved. Emergency resuscitation
equipment and medications were kept ready throughout the procedure. A Holter rhythm
monitor was placed before insertion of the probe, and recording was stopped after the retrieval
of the probe. Following an 8-hour-long fast, TEE was performed on patients in the left
decubitus position by a cardiologist using Vivid S5, General Electric, USA.

**Sedation:**

Group T and the other two study groups received local anesthesia in the oropharynx
region with 2 puffs of 1% lidocaine spray. In Group D, before insertion of the probe, the
patients were sedated with midazolam at a dose of 0.05 mg/kg iv (to achieve a Ramsay
Sedation Score of 2-3; see Appendix, about RSS). If needed, additional iv doses (0.005
mg/kg) were given during the procedure. The patients were kept under observation for 30-45
min. after the procedure. Their hemodynamic and respiratory parameters were monitored.

**Hypnosis:**

Hypnosis was performed by the same anesthesiologist hypnotized all of the patients
according to indirect Erickson’s method [15]. The first hypnotic induction was carried out the
day before the procedure. The hypnotic state was described to the patient as a state of mental
focus on a pleasant life experience. The word “hypnosis” was intentionally not used, in order
to avoid creating a positive or negative bias based on preconceived notions; instead, they were
told that they were undertaking sessions of “encouragement” and “mental preparation” for the
procedure. The next day, fifteen minutes before the procedure, another induction was
performed, and hypnosis was deepened. Every effort was made to produce a state of hypnosis
in which only ideas of relaxation and wellness were suggested to the patients during the
procedure.

**Analysis of heart rate variability parameters:**
All of the patients had Holter monitors on before swallowing the probe, and recording was terminated after the retrieval of the probe. Recordings were taken for 12-15 minutes, on average. Holter ECGs were analyzed using the CustoMed Holter system. The authors, blinded to the diagnosis of the patients, conducted the analyses of the Holter ECGs. The HRV analysis was assessed over a period and was performed in time and frequency domains according to the European Society of Cardiology/North American Society of Pacing and Electrophysiology guidelines. The following time domain parameters were calculated: mean of all normal RR intervals (mean RR); standard deviations of all NN intervals (SDNN); standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN); the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD); the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50). The spectral analysis of HRV included total power, which represents the variability of the entire signal and is obtained by summing the powers of each frequency band, the high-frequency (HF) component (0,15-0,40 Hz) and the low frequency (LF) component (0,04-0,15 Hz). The low-frequency power/ high-frequency power (LF/HF) was calculated in all subjects.

**Statistical analysis**

For statistical analyses, the NCSS (Number Cruncher Statistical System) 2007 & PASS 2008 Statistical Software (Utah, USA) programs were used. When the study data were evaluated, in addition to the descriptive statistical methods (mean, standard deviation), a OneWay Anova test was used for the comparisons of quantitative data and intergroup comparisons of parameters with a normal distribution. For intergroup comparisons of parameters that do not have a normal distribution, the Kruskal Wallis test was used; the Mann Whitney U test was used for the identification of the group that was different. The chi-square
test was used for the comparisons of qualitative data. The statistical significance level was $p<0.05$.

**RESULTS:**

The study was performed on 76 patients. There were 37 (48.7%) male and 39 (51.3%) female patients. The age range of the patients was between 18-83 years with a mean of $37.2 \pm 14.3$ years. The patients were analyzed as three groups: “D” (n=23), “T” (n=26) and “H” (n=27). There was no statistically significant difference between the mean ages and gender distributions of the groups ($p>0.05$) (Table 1 and 2).

Based on the means of systolic arterial pressure measurements (SAP) at the beginning and at 1 and 3 minutes, there was no statistically significant difference among the groups ($p>0.05$); however, the mean SAP of Group D at 5 and 10 minutes was significantly lower compared to other two groups ($p<0.05$) (Table 3). The means of the diastolic arterial pressure (DAP) at the baseline and at 1, 3, 5 and 10 minutes did not differ significantly among the groups ($p>0.05$); however, group D had lower levels compared to the other groups.

In Group D, compared to SpO$_2$ measurements at the beginning, the decreases seen in mean SpO$_2$ levels at 1,3,5 and 10 minutes was significant ($p<0.01$), but this was not the case for the other groups (Table 4).

The maximum heart rate and mean heart rate were lower in the hypnosis group compared to the two other groups. However, the means of maximum HR, mean HR and minimal HR did not differ significantly among the groups ($p>0.05$). The means of the SDNN of the HRV time domain parameters and the SDANN levels did not differ significantly among the groups ($p>0.05$); however, there were statistically significant differences among the pNN50 levels of the
groups (p<0.01). The pNN50 levels of Group D were significantly lower than those of Group T (p:0.002) and Group H (p:0.001) (p<0.01). There was no significant difference between the pNN50 levels of Groups T and H (p>0.05). There was a significant difference between the RMSSD levels of the groups (p<0.01). The RMSSD levels of Group D was significantly lower than those of Groups T (p:0.04) and H (p:0.001) (p<0.05, p<0.01, respectively). There was no significant difference between the RMSSD levels of Groups T and H (p>0.05) (Table 5).

Of the HRV frequency domain parameters, the means of the LF were lowest in Group H, but there was no significant difference among the groups as concerns this parameter (p>0.05). Similarly, the means of the HF was highest in Group H, but there was no statistically significant difference among the groups (p>0.05). LF/HF levels differed significantly among the groups (p<0.01). The LF/HF levels of Group H was significantly lower than Groups D (p:0.001) and T (p:0.001). There was no significant difference between the LF/HF levels of Groups T and D (p>0.05). The mean SPC and mean VPC levels of the groups did not differ significantly (p>0.05) (Table 4).

DISCUSSION:
While causing emotional stress and inducing a gag reflex, TEE also causes changes in the heart rate, blood pressure and O\(_2\) saturation [1,4]. The stress response is a complex action-reaction response resulting from several exogenous and endogenous stimuli. The stress response is sometimes handled through the sympathetic nervous system, resulting in increases in the heart rate and blood pressure of the individual concerned [16].

In our study, the maximum and mean heart rate was found to be the highest in Group D, who used midazolam, and the lowest in the hypnosis group; yet, there was no statistically significant difference among the three groups (p:0.05). In their studies, Blondheim et al.[3]
found that when the group sedated with midazolam was compared to the topical anesthesia group, there was a significant increase in the heart rate. Tachycardia during TEE results from stress. Because midazolam is an anxiolytic, we anticipated a decrease in tachycardia with its use; however, its demonstration of an opposite effect can be evaluated as a reflex increase resulting from its systemic vascular resistance reducing potential [3]. On the other hand, hypnotic intervention has been shown to yield variable cathecolamine and cortisol responses [17]. In a study that dramatically demonstrated that individual variability was closely related to hypnotic intervention, heart rate was decreased with a deep relaxation suggestion. As anxiety rates decreased, the cathecolamine levels returned to normal. In the hypnosis group, there was no significant decrease in blood pressure or O\textsubscript{2} saturation. Although it was not of statistical significance, the blood pressure levels of the midazolam group were lower compared to other groups, and O\textsubscript{2} saturation also decreased significantly (p<0.01). This can be explained through the depressive effects of midazolam on blood pressure and O\textsubscript{2} saturation. However, hypnotic sedation did not show a significant depression either on hemodynamics or ventilation [3,18].

HRV reflects the effects of the autonomic nervous system on sinus node activity. HRV is a complex measurement of heart rate modulation that encompasses sympathetic effects, parasympathetic effects and interactions thereof. In the time-domain analysis, the SDNN represents a general measurement of autonomic nervous system balance and is related to the total power. The SDANN reflects the long-term components of HRV that are mediated by both sympathetic and parasympathetic influences, while the RMSSD reflects the short-term components of HRV that are mediated by parasympathetic respiratory variations [19,20]. pNN50 is primarily an indices of parasympathetic tone. In our study, in the hypnosis group, both the SDNN and SDANN showed increases compared to the other two groups despite not reaching the level of statistical significance (p:0.39, p:0.30, respectively); PNN50 and
RMSSD had statistically significant increases in the hypnosis group (p:0.001, p:0.006). Increases in the RMSSD and PNN50 parameters in the hypnosis group indicates increased parasympathetic and decreased sympathetic nervous system activity. This demonstrates that sedation with midazolam does not decrease sympathetic activity.

In the frequency domain analysis, the LF mainly represents the sympathetic nervous system and the HF mainly reflects the parasympathetic nervous system. Frequency domain methods are preferred to time domain methods when investigating short-term recordings[19,21]. In our study group, in the frequency domain analysis, the LF parameter was lower in the hypnosis group compared to the midazolam and topical groups, whereas the HF was higher but not significant. The LF/HF rate was significantly lower in the hypnosis group compared to the other two groups. In their study, Aubert et al.[21] found that in healthy individuals, the LF levels were decreased in the hypnosis group while that of HF was increased and that of the LF/HF rate was decreased. DeBenedittis et al.[23] found similar results in healthy individuals undergoing hypnosis. Baglini et al.[13] demonstrated that the increase in sympathetic activity during a transluminal coronary angioplasty could be decreased with hypnosis but not with benzodiazepines. Our findings are in parallel with these studies, and our study demonstrates that hypnosis affects heart rate variability, shifting the balance of the sympathovagal interaction toward an enhanced parasympathetic activity, concomitant with a reduction of the sympathetic tone. Hypnosis decreases the central signaling of nociceptive stimuli at different levels [24]; moreover, cortical and subcortical correlates of autonomic activation have been found [25,26]. In particular, inhibition of serotonergic neurons during animal hypnosis have been demonstrated, and this type of neuron, whose activation accompanies sympathoexcitation, has been found in spinal cord and brainstem regions known to be involved in autonomic regulation [26,27].
Winn et al. [28] demonstrated that midazolam showed dominant sympathetic effects during the sedation period. The main effects of benzodiazepines are sedation, decreased anxiety, anterograde amnesia, and centrally mediated muscle relaxation. In addition to their actions on the central nervous system, benzodiazepines have a dose-dependent ventilatory depressant effect, and they also cause a modest reduction in arterial blood pressure and an increase in the heart rate as a result of a decrease in systemic vascular resistance. These drugs are known to act predominantly on cortical prefrontal areas and can inhibit the sympathetic drive by weakening emotional and perceptive mechanisms [29,30].

In conclusion, in TEE patients, the autonomic tone was significantly modified with hypnosis but not with midazolam sedation. Hypnotic sedation achieves this by increasing parasympathetic activity, decreasing sympathetic activity and changing the balance of sympathovagal interaction.

Appendix:

Ramsay Sedation Scale (RSS):

1. anxious and agitated or restless, or both
2. co-operative, oriented, and calm
3. responsive to commands only
4. exhibiting brisk response to light glabellar tap or loud auditory stimulus
5. exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6. unresponsive
REFERENCES:


5. Sutaria N, Northridge D, Denvir M. A survey of sedation and monitoring practices during


Additional files provided with this submission:

Additional file 1: TEE TABLE REVZION.doc, 77K
http://www.biomedcentral.com/imedia/9414677286618486/supp1.doc
Additional file 2: TEE- REVIEWER 1.doc, 23K
http://www.biomedcentral.com/imedia/1420986744660847/supp2.doc
Additional file 3: TEE-RE¿VEWER2.doc, 25K
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