Chronic Stimulation of the Left Vagus Nerve in Epilepsy: Balance Effects

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ABSTRACT: ***Background:*** Stimulation of the left vagus nerve (VNS) has been shown to control seizures in double blinded crossover studies in man. Animal studies have reported vagal afferent induced depression of nociceptive and motor reflexes which may be caused by an effect on the descending reticular system controlling spinal cord function. Anticonvulsant drug therapy may cause postural instability. The effects of VNS are assessed not only from the perspective of seizure control but also from the view of potential harm to other bodily systems. Long term (2¼ years) effects of VNS were compared to postural stability analyses. ***Methods:*** 8 subjects, 2 were females, mean age 34.5 ± 8.23 SD years, with intractable complex partial seizures, taking 3 anticonvulsant drugs were assessed for postural stability in quiet standing and while moving forwards, backwards and sideways with eyes open (EO) and eyes closed (EC). Data were collected and collated using an AMTI Biomechanics immovable forceplate, Newton M.A. U.S.A. The study design was longitudinal with pre-operative baseline data collected prior to neurostimulation and at intervals post operatively. ***Results:*** 4/8 balance measures showed significant changes from pre-operative values and after 2¼ years of stimulation. Area of sway (EO) in quiet standing $p = .022$ and total sway (EC) in the moving state $p = .019$ and total sway (EC) in quiet standing showed an increase in sway $p = .003$. Area of sway (EC) $p = .004$ tended to decrease. Regression analysis for frequency of stimulation showed an increase in sway with higher frequencies $T = 1.99$, $P = .05$. ***Conclusion:*** Chronic VNS does not augment postural instability.

RÉSUMÉ: Stimulation chronique du nerf vague gauche dans l'épilepsie: effet sur l'équilibre. ***Introduction:*** Des études chez l'homme en double insu avec chassé croisé ont démontré que la stimulation du nerf vague gauche (SNV) contrôle les crises d'épilepsie. Les études chez l'animal ont montré une dépression des réflexes nociceptifs et moteurs, induite par des afférents du vague, qui pourrait être causée par un effet sur le système réticulé descendant contrôlant la fonction de la moelle épinière. La pharmacothérapie anticonvulsivante peut causer une instabilité posturale. Nous évaluons les effets de la SNV non seulement du point de vue du contrôle des crises mais aussi du point de vue de dommages potentiels à d'autres systèmes. Nous avons comparé les effets à long terme (2¼ ans) de la SNV au moyen d'analyses de la stabilité posturale. ***Méthodes:*** On a évalué la stabilité posturale de 8 sujets, 2 femmes et 6 hommes, dont l'âge moyen était de 34.5 ± 8.23 ans, qui avaient des crises partielles complexes résistantes au traitement et qui prenaient 3 anticonvulsivants. Ils étaient évalués à la station debout stable et à la marche vers l'avant, vers l'arrière et de côté, les yeux ouverts (YO) et les yeux fermés (YF). Les données ont été recueillies et vérifiées au moyen d'une plaque ergométrique fixe AMTI de Biomechanics, Newton M.A. U.S.A. Il s'agit d'une étude longitudinale, les données de base préopératoires étant recueillies avant la neurostimulation et périodiquement en postopératoire. ***Résultats:*** On a observé des changements significatifs dans 4 mesures de l'équilibre sur 8 par rapport aux données préopératoires et après 2¼ années de stimulation. L'aire d'oscillation (YO) en position debout stable $p = 0.022$, l'oscillation totale (YF) en mouvement $p = 0.019$ et l'oscillation totale (YF) en position stable ont montré une augmentation de l'oscillation $p = 0.003$. L'aire d'oscillation (YF) $p = 0.004$ avait tendance à diminuer. Une analyse de régression pour la fréquence de la stimulation a montré une augmentation de l'oscillation à plus hautes fréquences $T = 1.99$, $p = 0.05$. ***Conclusion:*** La stimulation chronique du nerf vague n'augmente pas l'instabilité posturale.

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Motor control deficits, involving postural instability mechanisms such as ataxia and an increase in falling, in epileptic subjects are usually attributed to either anticonvulsant medication effects and/or to the natural history of epilepsy. The impact of the use of long term medications has shown deficits in other motor control performance measures (center of pressure) in upright stance in epileptic subjects when compared with normal subjects and those with Parkinsons disease (Figure 1).[1] Postural

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stability in upright stance is a model of complex motor control mechanisms involving higher central nervous system centers and peripheral nervous system inputs. The role of the monosynaptic spinal cord reflexes (knee jerk) and long latency reflexes in motor control (postural stability) are well known[2] as is the function of skeletal muscle. The role of the autonomic nervous system (ANS) in motor control (posture in upright stance) is only partially understood. However, the relationship between the autonomic and central nervous systems in motor control (strength and performance) is well established.[3,4] Probable relationships between the central nervous system and autonomic nervous system on activities involving finely tuned complex motor control in upright stance are not clearly understood despite early studies[5] which showed that afferent autonomic impulses produce reflex effects on skeletal muscle. Other animal experiments have also shown that stimulation of the central end of the mesenteric nerve produced contraction of the abdominal wall and of limb muscles.[6] Depressed knee jerk responses in anaesthetized animals with stimulation of the vagus nerve have been reported as well as experiments[7] showing depressed knee jerk responses and decreased frequency of action potentials in the resting quadriceps muscle after raising the carotid sinus pressure.[8] Further progress in understanding these mechanisms has been limited by the fact that most assessments of autonomic function are not predictable and there is considerable variability in the tests. (e.g., galvanic skin response). Further, most tests are indirect while vagal nerve stimulation (VNS) provides a direct method for assessing ANS. The implications from these early experiments are that afferent impulses in autonomic nerves may spread to many pathways in the central nervous system and affect lumbar somatic centers and reflexes. It is well known that the vagal nerves in the neck consist of 80% afferents.[9,10] It has also been demonstrated that the autonomic nervous system has an integrated afferent/efferent system which has been shown in cardiac studies of beat to beat variability. It has long been demonstrated that there are sympathetic afferents on skeletal muscle and it is reasonable to assume that there is also parasympathetic (ß receptor) control both centrally and peripherally.[11] Further, the main outflow of the vagal nucleus is to the vestibular system (a major contributor to motor control in upright stance) and there are known interactions between the vagal and vestibular systems. In some ways, the autonomic nervous system provides a platform upon which the rest of the nervous system acts. Postural stability is central to all activities of daily living.[12] VNS has provided an opportunity to assess potential linkages between autonomic, central and peripheral neurological effects.

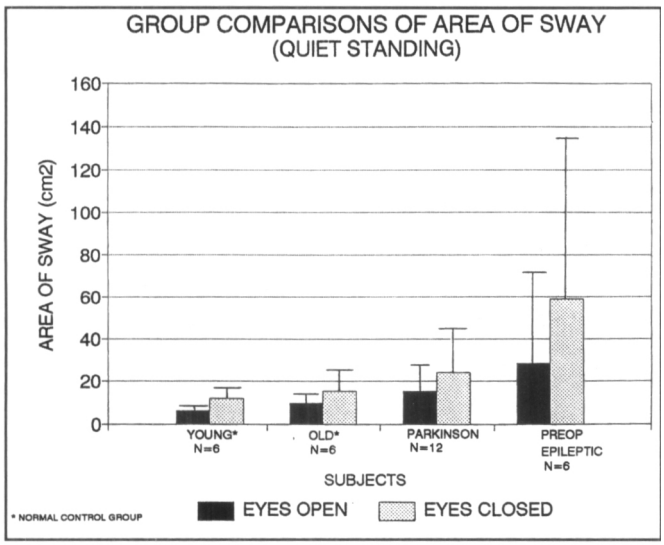

Figure 1: *Comparison of area of sway, in quiet standing state of young,* (mean age 27.3 ± 4.48 SD years), old,* (mean age 68.8 ± 4.75 SD years), parkinsonian subjects, (mean age 67.8 ± 4.92 SD years), and epileptic subjects, (mean age 33 ± 9.17 SD years).*

Previous efficacy studies of VNS in epileptic subjects have used postural stability analyses as an indicator of motor control. Center of pressure measures have been reported to be a reliable measure of impaired motor control (stability) in upright stance.[13,14] To quote Hasan et al. 1996, "center of pressure is the position of the applied force vector that is influenced by the shear force produced by body segment accelerations. Its displacements are a reaction to body dynamics and follow the neuromuscular control signal manifest vs. the vector of joint torques acting to position the center of gravity and preserve a stable position." The early studies of the acute effects of VNS on postural stability/motor control have shown no significant adverse affects which could be attributed to VNS.[1,15,16] A longitudinal study of 8 subjects with intractable complex partial seizures who received neurostimulation of the left vagus nerve were assessed for changes in postural stability. Long term stimulation (28 months) effects are reported below.

This work was done at McMaster University Medical Centre, Department of Neurology, Hamilton, Ontario, Canada. The project was approved by the Medical Ethics Committee of McMaster University Medical Centre and was supported by the Michael DeGroote Foundation for Epilepsy research.

Methods

Eight subjects (6 males, 2 females) with intractable complex partial seizures were implanted with a Neurocyberonics pacemaker Model 100, Cyberonics Inc. Webster, Texas, U.S.A. The mean age of the subjects was 34.5 ± 8.23 S.D. years (range 21-49 yrs), and all had complex partial seizures for more than 20 years. Inclusion criteria were that subjects must have had at least 6 seizures/month with no more than 14 days between seizures. All subjects were on 3 anticonvulsant drugs which consisted of combinations of valproic acid, carbemazepine, phenytoin, phenobarbital and dosages were not altered during the study. Levels were therapeutic throughout all trials. Exclusion criteria included evidence of any other neurological disorder or pregnancy. All subjects were their own controls and any disturbances in sway due to medications or previous disorders remained constant. Postural Stability (motor control) was assessed with an AMTI Biomechanics immoveable forceplate, Newton, MA. U.S.A. Subjects stood on the forceplate for 30 seconds. Measures of postural sway (center of pressure measures) were done with eyes open and closed, while standing still and then while moving forward, backward and from side to side. Foot placement was constant. This paper will report the results of center of pressure measurements expressed clinically as total sway/velocity (cm/sec) and area of sway (cm^2). Please see Table 1 for an explanation of abbreviations used. The study design was a longitudinal double blinded cross over study. Subjects

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Table 1: Postural Stability Terminology.

Stability measures	Abbreviation
Area of sway, eyes open, quiet standing (cm^2)	AEOQS
Area of sway, eyes closed, quiet standing (cm^2)	AECQS
Total sway, eyes closed, quiet standing (cm/sec)	TSWECQS
Total sway, eyes closed, moving (cm/sec)	TSWECMV

were randomized into high (30 Hz at 500 μsec) and low frequency (1 Hz at 130 μsec) stimulation groups for 20 weeks after which they were all switched to the high frequency group.[17] Data were collected pre-operatively (Session 1; S1) and at 6-8 week intervals (S2-S3) and every 6 months thereafter (S4-S6), over 28 months. Each session involved assessment at half hour intervals over a 7 hour period. Each test set took 10 minutes. There were 6 sessions per subject. Complete data sets were available for 7 of the 8 subjects because 1 subject had compliance problems. There were 60 observations per subject. Data were analyzed with a repeated measures of covariance technique with 2 within subject factors, day, (repeated visits) and time of day (am to pm). A regression analysis approach was used to determine the effects of frequency of stimulation (High or Low). A coefficient of variation (CV) analysis was done to compare the variation between the parameters relative to the mean. The calculation is:

$$CV = \frac{\text{standard deviation of the test scores}}{\text{mean of the test scores}}$$

Results

An analysis of covariance showed statistically significant differences for 4 out of 8 stability measures for session to session changes (adjusted for pre-operative differences). The four variables were; area of sway with eyes open, while standing quietly, (AEOQS) p = .022, area of sway with eyes closed in the quiet standing state, (AECQS) p = .004, total sway (velocity) with eyes closed in quiet standing, (TSWECQS) p = .003, and total sway with eyes closed while moving, (TSWECMV) p = .019. In 3 of the 4 measures, results indicated an increase in postural sway while in 1 situation, area of sway, eyes closed while standing still, (AECQS) there was a decrease in sway. Analyses for the time of day factor showed no significant differences. While standard deviations are large, the coefficient of variation analysis results show that the variance about the mean is small and repeatable between sessions. These results indicate that individual performance was stable over sessions (Figure 2).

Regression analysis results showed a value for stimulation frequency T = 1.99, p = .05 indicating that the higher the frequency of stimulation the subject received, the greater the movement.

Discussion

Chronic stimulation of the left vagus nerve does not produce significant adverse effects on postural stability/motor control (Figure 3). In the quiet standing situation, with eyes open, the subjects swayed and this is an indication of a lack of motor control (AEOQS). However, with eyes closed, there was evidence of better control as demonstrated by the fact that while area of sway decreased, total sway increased. That is, the subjects may have been more aware of their loss of motor control and over corrected for this instability (Figure 4). In addition, total sway values for both eyes open and closed are very similar showing little variation between sessions. In the moving mode, total sway with eyes closed, analyses showed that subjects were able to make considerable corrections to the movement, once again indicating a greater awareness of a loss of balance and the need for correction. There was no evidence that performance was

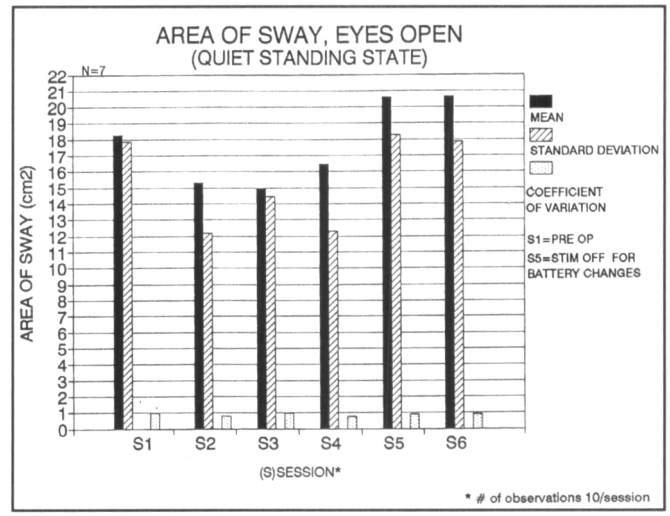

Figure 2: *An example of the relationship between the mean values, standard deviation and coefficient of variation for area of sway, eyes open, in quiet standing state over repeated sessions shows that while standard deviations are large, the variance around the mean is small and repeatable from session to session.*

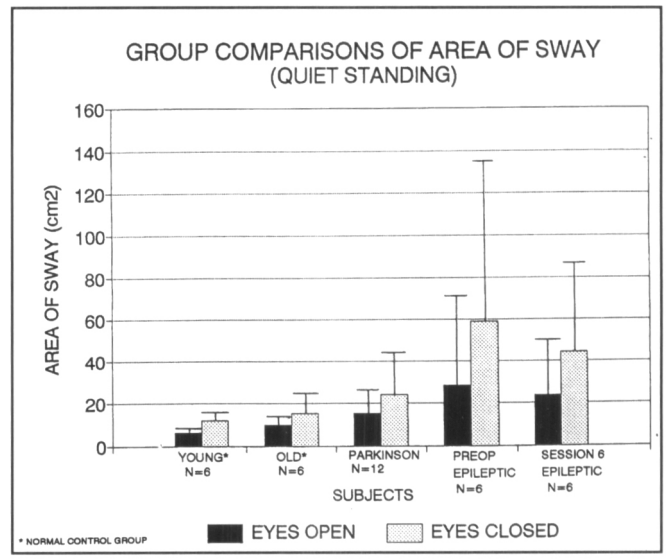

Figure 3: *Comparison of area of sway, in quiet standing state between normal control subjects, parkinsonian subjects and epileptic subjects pre-implant and after 2¼ years of VNS.*

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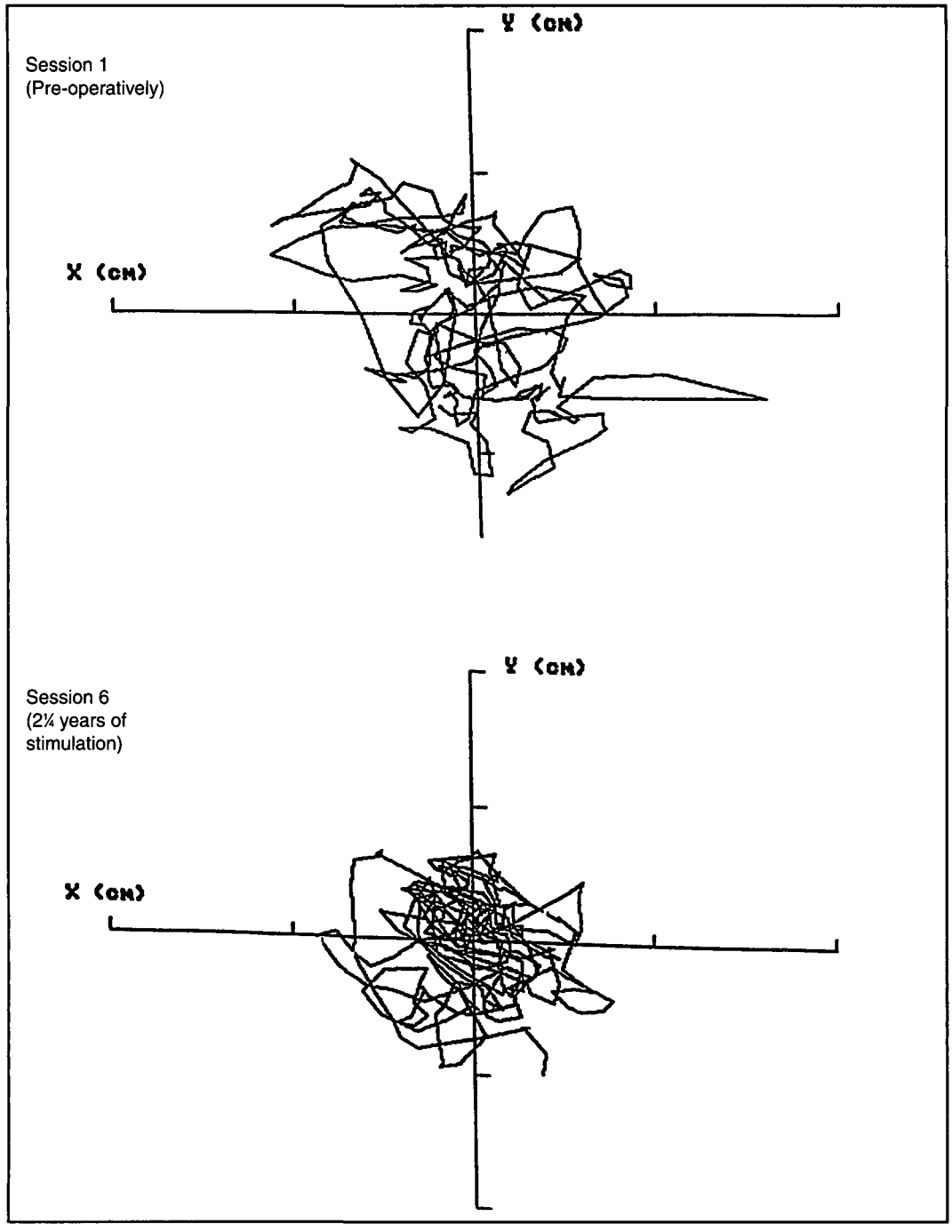

Figure 4: *Example of changes in motor control over time. Note the changes in circumference of plot and increased density (over corrections).*

significantly better in the morning or afternoon which might have been the case if there had been fluctuations in anticonvulsant drug levels throughout the day or had there been an effect due to circadian rhythms. There were no significant day to day variations as determined by the repeated measures of covariance technique. These findings are cautiously interpreted as a positive awareness and improvement in motor control in upright stance. The statistically significant results are not likely to be due to chance because the repeated measures analysis of covariance design with 2 within subject repeated factors, session and time of day (am-pm) greatly reduce the possibility of finding statistically significant results for each of the balance measures. Using subjects as their own control in this study is valid because the within subject variance is accounted for in the design.

It may be that adverse effects in some stability measures are due to the natural history of chronic complex partial seizures and the long term effects of anticonvulsant drugs. Others,[18-21] have found balance disturbances in epileptic subjects attributable to diphenylhydantoin effects and long term use of anticonvulsant medication polytherapy. Animals studies,[22-24] have

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have indicated that balance disturbances in epilepsy may be related to cerebellar Purkinje cell loss. This study has shown that chronic stimulation of the left vagus nerve has not produced significant adverse effects on motor control.

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