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RELATIONSHIP BETWEEN ULTRASONOGRAPHIC, ELECTROMYOGRAPHIC AND CLINICAL PARAMETERS IN ADULT STROKE PATIENTS WITH SPASTIC EQUINUS: AN OBSERVATIONAL STUDY.

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ABSTRACT

Objective – To find more accurate indices that could affect decisions in spasticity treatment by investigating the relationship between ultrasonographic, electromyographic, and clinical parameters of the gastrocnemius muscle in adults with spastic equinus after stroke.

Design – Observational study.

Setting – Two university hospitals

Participants – Forty-three chronic stroke patients with spastic equinus.

Interventions – Not applicable.

Main Outcome Measures – Ultrasonographic features were: spastic gastrocnemius muscle echo intensity, muscle thickness, and posterior pennation angle of the gastrocnemius medialis and lateralis in both legs. Electromyographic evaluation included compound muscle action potential recorded from the gastrocnemius medialis and lateralis of both legs. Clinical assessment of the spastic gastrocnemius muscle was performed with the modified Ashworth scale and by measuring ankle passive dorsiflexion range of motion.

Results – Spastic muscle echo intensity was inversely associated with proximal (gastrocnemius medialis and lateralis: P=0.002) and distal (gastrocnemius medialis and lateralis: P=0.001) muscle thickness,

pennation angle (gastrocnemius medialis: P<0.001; gastrocnemius lateralis: P=0.010), compound muscle action potential (gastrocnemius medialis: P=0.014; gastrocnemius lateralis: P=0.026), and ankle passive dorsiflexion range of motion (gastrocnemius medialis: P=0.038; gastrocnemius lateralis: P=0.024). The pennation angle was directly associated with the proximal (gastrocnemius medialis and lateralis: P<0.001) and distal (gastrocnemius medialis: P=0.001; gastrocnemius lateralis: P<0.001) muscle thickness of the spastic gastrocnemius muscle. The modified Ashworth scale score was directly associated with muscle echo intensity (gastrocnemius medialis: P=0.039; gastrocnemius lateralis: P=0.027) and inversely related to the pennation angle (gastrocnemius medialis and lateralis: P=0.001), proximal (gastrocnemius medialis: P=0.016; gastrocnemius lateralis: P=0.009), and distal (gastrocnemius lateralis: P=0.006) muscle thickness of the spastic gastrocnemius.

Conclusions – Increased spastic muscle echo intensity was associated with reduced muscle thickness, posterior pennation angle, and compound muscle action potential amplitude in the gastrocnemius muscle. Building on previous evidence that these instrumental features are related to botulinum toxin response, these new findings may usefully inform spasticity treatment decisions.

INTRODUCTION

Spasticity, a common motor dysfunction arising from upper motor neuron lesions,[1] affects between 17% and 42.6% of patients with chronic stroke, with a substantial impact on the continuum of rehabilitative care and recovery.[2, 3] According to Lance,[4] spasticity refers to a motor disorder characterized by a velocity-dependent increase in tonic stretch reflex (muscle tone), with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex as one component of upper motor neuron syndrome. Patients with spastic paresis are disabled by paresis (reduced voluntary recruitment of skeletal motor units), soft tissue contracture, and muscle overactivity (reduced ability to relax muscles).[5, 6] Muscle contracture in spastic paresis includes atrophy (loss of muscle mass), loss of sarcomeres (shortening), accumulation of intramuscular connective tissue, increased fat infiltration, and modifications at the myotendinous junction.[5] Degenerative alterations of muscle properties not only interfere with motor function recovery but also increase the degree of spasticity and further aggravate motor impairment.[2, 7] Moreover, progressive changes in the spastic muscle may account for the loss of response to botulinum toxin type A therapy,[8] which is considered a first-line treatment for patients with focal spasticity.[9]

Ultrasonography studies to examine disruptions in the normative architecture of spastic muscles have documented changes in gastrocnemius muscle thickness, fascicle length, pennation angle, and echo intensity in patients with ankle spasticity consequent to chronic stroke.[10, 11] Such structural modifications are associated with the clinical features of spastic equinus, including triceps surae muscle stiffness and ankle joint range of motion.[10, 11] In addition, spastic gastrocnemius muscle echo intensity has been shown to relate to the therapeutic response to botulinum toxin type A injection,[11] the in vivo efficacy of which can be measured by the compound muscle action potential (CMAP) amplitude, an electromyographic parameter of muscle fiber contraction that quantifies the suppressive action of the botulinum toxin on neuromuscular transmission.[12, 13]

From this basis, a better understanding of the association between instrumental and clinical features of muscle spasticity may usefully inform clinicians in the appropriate selection of therapeutic approach and improve treatment of spasticity.[9] The main aim of this study was to investigate the relation between ultrasonographic and electromyographic parameters measured at the gastrocnemius muscle in adult patients with spastic equinus foot resulting from stroke. The secondary aim was to

further examine the association between instrumental and clinical features of spasticity in patients with stroke.

METHODS

This was a 2-center observational study. The inclusion criteria were as follows: age >18 years, spastic equinus foot consequent to first-ever unilateral ischemic or hemorrhagic stroke (documented by a computerized tomography scan or magnetic resonance imaging; subarachnoid hemorrhage excluded), gastrocnemius muscle spasticity grade of at least 1 on the Modified Ashworth Scale (MAS),[14] at least 6 months since stroke onset, and no botulinum toxin injection into the affected leg muscles or rehabilitation treatment in the 5 months before recruitment. Exclusion criteria were as follows: fixed contractures involving the affected leg, bony deformities of the lower limbs, previous neurolytic or surgical treatment for spasticity of the affected leg, and other neurologic or orthopedic conditions affecting the lower limbs (bilateral stroke, peripheral neuropathy, peripheral nerve lesion, myopathy, severe osteoarthritis, recent muscle lesion, recent bone fracture, joint replacement). All participants were outpatients and gave their informed consent to participate in the study. The study was carried out according to the Declaration of Helsinki and was approved by the local ethics committee.

Ultrasonographic evaluation

Patients underwent real-time B-mode ultrasonography performed with a linear transducer (scanning frequency of 10MHz)[a] positioned perpendicular to the gastrocnemius surface and placed gently over the skin using water-soluble transmission gel to avoid pressure-induced alterations of the muscle tissue.[11] The following ultrasonographic features were evaluated: muscle echo intensity, muscle thickness, and posterior pennation angle. Patients remained in the prone position with their legs outstretched during the procedure. A board of 2 physicians (1 at each center) with >5 years experience in skeletal muscle ultrasound imaging examined all patients (the same ultrasound machine model was used at both centers). The examiners were blind to the electromyographic and clinical evaluations.

Muscle echo intensity was visually evaluated in the transverse view at each head of the spastic gastrocnemius muscle (the transducer was positioned over the midbelly of the muscle bulk) and graded semiquantitatively according to the Heckmatt scale (grade I, normative; grade II, increase in muscle echo intensity while bone echo is still distinct; grade III, marked increase in muscle echo intensity and reduced bone echo; grade IV, very high muscle echo intensity and complete loss of bone echo).[11, 15, 16] This scale is a validated tool with an intraclass

correlation coefficient of 0.915 between raters and an intrarater intraclass correlation coefficient of 0.972.[17] A single examiner evaluated all the images and scored the muscle echo intensity in all patients.

Muscle thickness (distance from the superficial to deep aponeurosis) was measured at the gastrocnemius medialis (GM) and gastrocnemius lateralis (GL) of the affected and healthy legs.[18] The transducer was positioned in the transverse view at 2 sites: near the muscle origin (proximal site) and at the midbelly of the muscle bulk (distal site).[10, 18] The posterior pennation angle (angle between the orientation of muscle fascicles and superficial aponeurosis) was measured at each head of the spastic and healthy gastrocnemius muscle.[10] The transducer was positioned in the longitudinal view at 5cm from the muscle tendon junction.[10]

Electromyographic evaluation

The CMAP amplitude was recorded from each head of the spastic and healthy gastrocnemius muscle by supramaximal posterior tibial nerve stimulation (branches for the GM and GL) at the popliteal fossa of both legs by means of an electromyograph[b] and disposable silver/silver chloride surface electrodes with belly-tendon montage.[12, 13] An infrared lamp was used to maintain leg skin temperature >31°C during the

recording. Patients remained in the prone position with their legs outstretched during the procedure.

A board of 2 physicians (1 at each center) with >10 years of experience in electromyography performed all evaluations (the same electromyography machine model was used at both centers).

The examiners were blind to the ultrasonographic and clinical evaluations.

Clinical evaluation

The following clinical features of the affected leg were evaluated: ankle joint passive range of motion (PROM) and gastrocnemius muscle spasticity as measured by the MAS. Patients remained in the supine position with the knees fully extended during the evaluation. A board of 2 physicians (1 at each center) with >8 years of experience in the evaluation of spasticity performed all evaluations. The examiners were blind to the ultrasonographic and electromyographic evaluations.

Ankle PROM was measured using a handheld goniometer. The sensitivity of the measurement was arbitrarily at 5°. The dorsiflexion angle was defined as positive and the plantar flexion angle as negative, taking 0° as the neutral position of the joint.[19]

The MAS is a 6-point scale for grading the resistance of a relaxed limb to rapid passive stretch (0, no increase in muscle tone; 1, slight increase in muscle tone at the end of the range of motion; 1+, slight increase in muscle tone through less than half of the range of motion; 2, more marked increase in muscle tone through most of the range of motion; 3, considerable increase in muscle tone; 4, joint is rigid).[14] For statistical purposes, a score of 1 was considered as 1, and a score of 1+ was considered a 2 and so on, until 5.[20]

Statistical analysis

Statistical analysis was carried out using SPSS version 21.0.[c] The Wilcoxon signed-rank test was used to compare the instrumental parameter values between legs (affected vs. healthy) and muscles (GM vs. GL) within the same individual. The Spearman rank correlation test was performed to assess the association between instrumental and clinical features of the spastic gastrocnemius muscle. After dividing the patients into 3 groups according to their Heckmatt scale score, the Kruskal-Wallis test was used to verify the difference in the distribution of values for muscle thickness, posterior pennation angle, and CMAP amplitude between groups (GM and GL were analyzed separately). Multiple post hoc comparisons between groups were performed with

Mann-Whitney tests for muscle thickness, posterior pennation angle, and CMAP amplitude. The alpha level for significance was set at $P<0.05$. The Bonferroni correction was used for multiple comparisons; $P<0.016$ was set as the significance threshold.[21]

RESULTS

Between September 2012 and December 2013, 43 persons (28 men and 15 women; mean age, 61.3 years) with spastic equinus foot resulting from stroke (mean time since onset, 5.7 years) were recruited from among 101 consecutive outpatients with chronic stroke, 58 who were excluded according to the inclusion/exclusion criteria.

There were significant differences in gastrocnemius muscle thickness, posterior pennation angle, and CMAP amplitude in the affected leg compared with the healthy leg (table 1).

Comparison of the spastic GM versus the GL showed a significant difference in proximal muscle thickness (1.24±0.35 cm vs. 1.09±0.31cm; P=0.004), distal muscle thickness (1.07±0.44 cm vs. 0.91±0.44cm; P=0.004), posterior pennation angle (15.77°±6.37° vs. 13.6°±5.17°; P=0.004), and CMAP amplitude (6.47±4.24 mV vs. 4.95±2.7 mV; P=0.014), but not in muscle echo intensity (2.86±0.77 vs. 2.7±0.71; P=0.183).

The Spearman correlation showed a significant direct association between the spastic GM and GL for muscle echo intensity (P=0.014), proximal muscle thickness (P<0.001), distal muscle thickness (P<0.001), and CMAP amplitude (P<0.001). Spastic gastrocnemius muscle echo

intensity was inversely associated with proximal muscle thickness (GM: P=0.002; GL: P=0.002), distal muscle thickness (GM: P=0.001; GL: P=0.001), posterior pennation angle (GM: P<0.001; GL: P=0.01), CMAP amplitude (GM: P=0.014; GL: P=0.026), and ankle PROM (GM: P=0.038; GL: P=0.024). Furthermore, the posterior pennation angle was directly associated with proximal muscle thickness (GM: P<0.001; GL: P<0.001) and distal muscle thickness (GM: P=0.001; GL: P<0.001) of the spastic gastrocnemius. In addition, the MAS score was directly associated muscle echo intensity (GM: P=0.039; GL: P=0.027) and inversely associated with posterior pennation angle (GM: P=0.001; GL: P=0.001), proximal muscle thickness (GM: P=0.016; GL: P=0.009), and distal muscle thickness (GL: P=0.006) of the spastic gastrocnemius (table 2).

Multiple independent-sample Kruskal-Wallis tests showed an overall significant difference between groups (namely, Heckmatt scale grades II-IV) in the distribution of proximal muscle thickness (GM: P=0.011, χ^2=9.111; GL: P=0.005, χ^2=10.765), distal muscle thickness (GM: P=0.009, χ^2=9.424; GL: P=0.003, χ^2=11.515), posterior pennation angle (GM: P<0.001, χ^2=20.172; GL: P=0.005, χ^2=10.458), and CMAP amplitude (GM: P=0.04, χ^2=6.452; GL: P=0.002, χ^2=12.575).

Table 3 reports the results of the post hoc comparisons.

Table 1 – Affected vs. healthy leg comparisons (Wilcoxon signed ranks test).

Outcome measures	Muscle	Affected leg Mean (SD)	Healthy leg Mean (SD)	*P* value (Z)
Muscle thickness - proximal site (cm)	GM	1.24 (0.35)	1.56 (0.30)	<0.001* (-5.007)
	GL	1.09 (0.31)	1.32 (0.25)	<0.001* (-4.627)
Muscle thickness - distal site (cm)	GM	1.07 (0.44)	1.40 (0.32)	<0.001* (-4.672)
	GL	0.91 (0.44)	1.09 (0.37)	<0.001* (-3.577)
Pennation angle (degrees)	GM	15.77 (6.37)	24.05 (6.07)	<0.001* (-5.527)
	GL	13.60 (5.17)	17.72 (6.11)	<0.001* (-3.804)
CMAP (mV)	GM	6.47 (4.24)	13.30 (6.31)	<0.001* (-5.713)
	GL	4.95 (2.70)	11.24 (5.35)	<0.001* (-5.308)

Abbreviations: *SD*, Standard Deviation; *GM,* Gastrocnemius medialis; *GL*, Gastrocnemius lateralis.
* Significant comparison ($P<0.05$)

Table 2 – Correlation matrix for study variables (Spearman's rho).

Outcome measures		Age	Sex	Time from onset	MAS	Ankle PROM	Muscle echo intensity		Posterior pennation angle		Proximal muscle thickness		Distal muscle thickness		CMAP	
							GM	*GL*	*GM*	*GL*	*GM*	*GL*	*GM*	*GL*	*GM*	*GL*
Age		1.000														
Sex		-0.030	1.000													
Time from onset		0.063	-0.044	1.000												
MAS		-0.002	-0.079	0.398*	1.000											
Ankle PROM		-0.214	0.088	-0.024	-0.229	1.000										
Muscle echo intensity	*GM*	0.186	0.082	0.177	0.316*	-0.318*	1.000									
	GL	0.285	0.097	0.092	0.338*	-0.344*	0.373*	1.000								
Posterior pennation angle	*GM*	-0.073	0.008	-0.138	-0.454*	0.160	-0.684*	-0.284	1.000							
	GL	-0.248	0.178	-0.165	-0.503*	0.230	-0.379*	-0.387*	0.697*	1.000						
Proximal muscle thickness	*GM*	-0.027	-0.112	-0.125	-0.365*	0.097	-0.464*	-0.088	0.687*	0.470*	1.000					
	GL	-0.131	-0.291	-0.084	-0.393*	0.166	-0.427*	-0.466*	0.568*	0.586*	0.527*	1.000				
Distal muscle thickness	*GM*	-0.197	-0.033	-0.119	-0.209	0.081	-0.473*	-0.059	0.487*	0.412*	0.678*	0.592*	1.000			
	GL	-0.213	-0.228	-0.081	-0.409*	0.250	-0.458*	-0.498*	0.580*	0.613*	0.480*	0.855*	0.600*	1.000		
CMAP	*GM*	0.032	-0.244	0.294	0.250	-0.127	-0.372*	0.202	0.089	-0.286	-0.008	-0.249	-0.064	-0.132	1.000	
	GL	-0.121	-0.199	0.212	0.156	0.087	-0.449*	-0.339*	0.237	0.034	0.117	0.045	-0.077	0.140	0.569*	1.000

Abbreviations: *MAS*, modified Ashworth scale; *PROM*, passive range of motion; *CMAP*, compound muscle action potential; *GM,* gastrocnemius medialis; *GL*, gastrocnemius lateralis.
* Significant correlation ($P<0.05$)

Table 3 – Post hoc comparisons in the Heckmatt scale.

Outcome measures	**Muscle**	**Heckmatt II** Mean (SD) GM (n=16) GL (n=18)	**Heckmatt III** Mean (SD) GM (n=17) GL (n=17)	**Heckmatt IV** Mean (SD) GM (n=10) GL (n=8)	**Between-group comparisons** Mann-Whitney test **Heckmatt III vs. II** *P* value (*Z*)	**Heckmatt IV vs. II** *P* value (*Z*)	**Heckmatt IV vs. III** *P* value (*Z*)
Muscle thickness – proximal site (cm)	GM	1.42 (0.17)	1.20 (0.35)	1.02 (0.44)	0.024 (-2.254)	0.010* (-2.588)	0.167 (-1.382)
	GL	1.19 (0.35)	1.08 (0.23)	0.79 (0.10)	0.083 (-1.735)	0.009* (-2.618)	0.004* (-2.878)
Muscle thickness – distal site (cm)	GM	1.30 (0.43)	1.02 (0.05)	0.78 (0.39)	0.055 (-1.915)	0.004* (-2.853)	0.107 (-1.614)
	GL	1.14 (0.48)	0.80 (0.31)	0.49 (0.06)	0.036 (-2.100)	0.011* (-2.558)	0.004* (-2.874)
Posterior pennation angle (degrees)	GM	21.13 (4.38)	13.82 (4.93)	10.50 (5.02)	<0.001* (-3.703)	<0.001* (-3.591)	0.065 (-1.845)
	GL	14.95 (4.61)	14.22 (5.00)	7.50 (3.15)	0.572 (-0.566)	0.002* (-3.148)	0.006* (-2.774)
CMAP (mV)	GM	7.92 (4.23)	6.68 (4.25)	3.81 (3.21)	0.407 (-0.829)	0.010* (-2.559)	0.083 (-1.734)
	GL	5.73 (3.10)	5.31 (1.54)	1.42 (0.94)	0.939 (-0.076)	0.002* (-3.060)	<0.001* (-3.536)

Abbreviations: *SD*, Standard Deviation; *GM,* Gastrocnemius medialis; *GL*, Gastrocnemius lateralis; *CMAP,* compound muscle action potential.
* = statistically significant (*P*<0.016).

DISCUSSION

We found a statistically significantly association between an increase in muscle echo intensity and a decrease in CMAP amplitude, muscle thickness, and posterior pennation angle of the spastic gastrocnemius muscle in this group of chronic patients with spastic equinus resulting from stroke. Compared with the healthy leg, the gastrocnemius muscle in the affected leg showed degenerative changes, including decreased posterior pennation angle, muscle thickness, and CMAP amplitude.

Clinical symptoms of spasticity have been reported to closely relate to such various changes in muscle structure as shortening of muscle fascicles, reduction of pennation angle, and increased echo intensity.[10, 11, 22-24] Our findings further confirm these previous observations and are in keeping with Gracies's description of the mechanisms underlying muscle contracture, including atrophy, shortening, and accumulation of intramuscular connective tissue and fat.[5, 6] In addition, the patients with grade II spastic gastrocnemius muscle echo intensity on the Heckmatt scale (i.e., increase in spastic muscle echo intensity while bone echo is still distinct) were noted to have a significantly greater CMAP amplitude, posterior pennation angle, and muscle thickness than those with higher muscle echo intensity (particularly those with Heckmatt

scale grade IV, ie, very high muscle echo intensity and complete loss of bone echo). To our knowledge, no previous studies to date have compared muscle thickness, pennation angle, and CMAP amplitude values distributed by echo intensity of the spastic gastrocnemius in patients with chronic stroke (see table 2).

Botulinum toxin acts in the cytosol of nerve endings where it inhibits the release of acetylcholine at the neuromuscular junction.[23] Progressive alteration of the contractile and structural properties of spastic muscles may lead to the loss of response to botulinum toxin type A therapy,[8] which is considered a first-line treatment to reduce muscle overactivity in adult patients with focal spasticity.[9] Our findings show a significant association between the instrumental features of the spastic muscle that previous studies found to be related to botulinum toxin response (muscle echo intensity, CMAP amplitude) and other ultrasonographic parameters used to quantify the changes in passive mechanical muscle properties (muscle thickness, pennation angle).[8, 10-13] In keeping with the observational study design, no treatment interventions were performed. We may hypothesize, however, that these ultrasonographic and electromyographic findings may be useful for making inferences about the clinical efficacy of botulinum toxin treatment and about whether it

may be less or not useful in patients with higher muscle echo intensity and lower muscle thickness, pennation angle, and CMAP amplitude.

In patients with spasticity, the increased resistance to passive movement is related to stretch reflex hyperactivity and nonreflex biomechanical changes in muscles.[23, 25] In a recent study, Picelli et al.[11] evaluated changes in gastrocnemius muscle echo intensity in patients with stroke and observed a significant association between the MAS and Tardieu Scale scores, ankle PROM, and spastic gastrocnemius muscle echo intensity in adult patients with spastic equinus foot consequent to stroke.[11] Here, we clinically evaluated patients by measuring ankle PROM according to the MAS. Ankle PROM was reported to correlate with changes in the passive mechanical properties of the spastic gastrocnemius muscle in patients with stroke.[23] The MAS evaluates spasticity by grading resistance to rapid passive movement, but it cannot differentiate between stretch reflex hyperactivity and nonreflex biomechanical changes in spastic muscles.[26] Our findings show that greater ankle PROM correlates with lower muscle echo intensity and that a lower MAS score correlates with a greater pennation angle, greater muscle thickness, and lower muscle echo intensity. This is in line with previous findings and the hypothesis that the MAS score and ankle PROM, because they quantify the changes in the passive properties of

muscles, may be correlated with structural alterations in the spastic muscle.[11] This concept is further confirmed by the significant association we found between clinical assessment and ultrasonographic findings.

Study limitations

This study has several limitations. First, the small sample size may have hindered evaluation of a gradient correlation between spastic gastrocnemius muscle echo intensity and other instrumental and clinical parameters in the post hoc comparisons and correlation analyses. Second, we restricted the electromyographic parameters to the CMAP amplitude because it is used to quantify the action of the botulinum toxin in vivo.[12, 13] From a therapeutic point of view, it would have been interesting to study its relation with the other instrumental features of spastic muscles (eg, echo intensity) associated with the response to botulinum toxin type A.[11] From a clinical point of view, evaluation of other electromyographic parameters (eg, Hoffmann reflex), the tendon, and stretch reflexes may have allowed for a more accurate interpretation of the present findings.[27] Third, the soleus muscle, which has been observed to be responsible for spastic equinus foot in 75% of cases,28 was not evaluated; therefore, our results could be more easily compared with those of previous studies in the same field (ultrasonographic

evaluation of structural changes in spastic muscles in association with clinical features of spastic equinus).[10, 11] Fourth, no sonoelastographic evaluation of spastic muscles was done. This innovative ultrasound-based technique is gaining interest from researchers and clinicians as a means to evaluate tissue elasticity in comparison with other instrumental and clinical parameters in the study of spasticity.[29]

To further validate our findings, larger scale studies, including more instrumental (electromyographic and ultrasonographic) features of spastic muscles, are desirable. A future area of focus would be the clinical application of these findings to predict the therapeutic effect of botulinum toxin type A therapy in patients with stroke with muscle spasticity.

CONCLUSIONS

An increase in muscle echo intensity was significantly associated with a decrease in CMAP amplitude, muscle thickness, and posterior pennation angle of the spastic gastrocnemius muscle in patients with chronic stroke. Building on previous studies that used these instrumental features to quantify changes in passive mechanical spastic muscle properties, which may be responsible for the loss of response to botulinum toxin type A,[8, 10-13] these new findings may usefully inform treatment decisions about how to improve spasticity in patients with chronic stroke.

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APPENDIX

Suppliers list

a. GE Logiq Book XP; GE Medical Systems, 4855 West Electric Ave, Milwaukee, WI 53215.
b. Oxford Medelec Synergy; Viasys Healthcare Inc, 5225 Verona Rd, Madison, WI 53711.
c. SPSS Statistical Package; SPSS Inc, 233 South Wacker Drive, Chicago, IL 60606.