行政院國家科學委員會專題研究計畫成果報告

（第二年期計畫）

計畫名稱： 以原始反射定量檢查評估腦中風病人復健預後之研究

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中　文　摘　要

　　　　原始反射也稱為胚胎反射或釋放反射，常出現於嬰兒時期之腦皮層抑制功能不足，在成長過程中逐漸消失，成人之後較不會出現，但會重新出現於嚴重散播型腦病變的病人身上，如癡呆症，帕金森氏病，腦中風及受傷性腦傷等，這些病人都有很高的發生率，而原始反射的再出現主要是較高中樞神經功能抑制失常，因此患者的學習能力也隨之降低。

　　　　由於過去的研究在原始反射的檢查上只限於定性的研究而無較客觀定量化的方法，本研究以台灣地區重要疾病腦中風收集三十八位病人作電生理神經反射檢查及智能檢查(Mini-Mental State Examination)，其中 snout 反射，頜反射(jaw jerk)和眉間 (glabellar) 反射以改良式反射檢查槌連接肌電圖儀器作檢查，眼角膜下頜 (corneomandibular) 反射則以自製檢查器連接肌電圖儀器，測量其反射傳導時間及肌肉反應波振幅大小，檢查結果顯示腦中風病人的頜反射，snout 反射，眉間反射及眼角膜下頜反射的出現率比同年齡正常人高，頜反射與 snout 反射之神經傳導時間在腦中風病人與正常對照組之間雖無明顯差異，但反應波振幅在腦中風病人則明顯增大(r=0.67, P<0.01)，而腦中風病人的智能指數也與 snout 反應波及眼角膜下頜反射之振幅大小成線性負相關 (依序為 P<0.05 和 P<0.05)。而梗塞型腦中風出現原始反射機率較出血性腦中風高，此與腦皮層受損造成認知障礙間接影響到病人復健過程的學習能力及治療預後有關。

　　　此研究結果顯示腦中風病人的原始反射隨智能的減退而增強，電生理神經檢查除了可提供一個較客觀且定量的方法外，也可直接由反應波大小所代表的神經軸量多寡，了解腦部失去抑制的程度，作為評估腦中風病人復健治療預後的指標。

關鍵字：原始反射，神經生理檢查，腦中風

ABSTRACT

Primitive reflexes as the synonyms of embryonic reflexes, release reflexes or cortical disinhibition responses are among the labels used for several reflexes which are common in fetal or infant life. They become less apparent in young adults, and then are seen again in old age or in patients with cortical deterioration. Since there are very less quantitative assessments available for primitive reflexes, we report the use of electrophysiological study for the quantitative measurement of reflex latencies and wave responses of primitive reflexes including jaw jerk, snout reflex, glabellar reflex, and corneomadibular reflexes in 38 patients with stroke. The preliminary results showed a significantly higher persistence in all primitive reflexes of stroke patients than in normal age controls. Wave amplitude of snout reflexes obtained in stroke patients is greater than those in normal controls (r=0.67, P<0.01). A regression relationship was noted between the wave amplitude of snout reflex and cognitive function of stroke patients. The persistence of primitive reflexes in infarctive stroke is higher than those obtained in hemorrhagic stroke patients.

These results suggest that the appearance of primitive reflexes is related to the nature of stroke involving brain function of dysinhibition. Activities or persistence of primitive reflexes are also correlated with the mentality of stroke patients which is the major factor affecting learning abilities in stroke rehabilitation. A conclusion was made that quantitative electrophysiological assessments of primitive reflexes may provide as a useful tool in evaluation of outcome in stroke rehabilitation.

Key words: Primitive reflex, electrophysiology, stroke

INTRODUCTION

Primitive reflexes, embryonic reflexes, release reflexes or cortical disinhibition responses are among the labels used for several reflexes which are present in the earliest stages of ontogenetic development.[1,2] These developmental, or primitive, reflexes are ubiquitously present in fetal life, in the new born and in infants, and gradually disappear with age[3]. It is hypothesized that primitive reflexes in mature subjects represent release phenomena, reflecting a decrease in higher cortical control over lower centres. Primitive reflexes existing in early stages of ontogenesis are suppressed as the brain matures, but may reappear in old age or in patients with cortical deterioration when cerebral inhibition decreases.

The clinical value of primitive reflexes in adults has not been established. There have been reports of various primitive reflexes to be pathognomonic for diseases such as Parkinson's disease[4,5] or dementia.[6,7] Several authors have argued that primitive reflexes may be indicative of the cerebral location involved. Diffuse hemispherical damage or focal, notably frontal, lesions have been mentioned in this respect. Some authors have claimed that there is a relation between primitive reflexes and specific neuropsychological dysfunctions and the degree of cognition deterioration[8]. Others question the value of primitive reflexes in a routine neurological investigation, arguing that primitive reflexes have no specific diagnostic value but are merely a sign of physiological aging.[9,10] The literature on the possible clinical relevance of primitive reflexes is thus inconclusive and unclear.

A major problem while comparing various studies on primitive

reflexes is that the values given for the prevalence and incidence of these signs vary among the publications. One of the important reasons for this may be the lack of standardization in elicitation of these reflexes. Most of the studies in primitive reflexes describes the presence or absence of the responses and shows the diversity in the assessments in scoring. The aim of the present study is to evaluate the primitive reflexes by electrophysiological approaches, and try to correlate the relationship between primitive reflexes and outcome of rehabilitation in patients with stroke.

SUBJECTS AND METHODS

Patient Profile

Thirty-eight patients, aged between 53 to 83 years (mean, 65.1 years) with clinical diagnosis of stroke were participated in this study. There were 25 men and 13 women. The disease duration from the onset of stroke to the time of evaluation is one month to two years. Stroke can be defined as rapidly developing clinical signs of focal (at times global) loss of cerebral function with symptoms lasting for more than 24 h with no apparent cause other than that of vascular origin (WHO definition). Ischemic cerebral infarction is defined as a stroke caused by infarction of cerebral tissue confirmed by computed tomography (CT), or, in patients with a clinically definite stroke, with a normal CT scan which exclude cerebral hemorrhage. Cerebral hemorrhage is defined as a stroke caused by spontaneous bleeding in the brain substance or ventricles and is confirmed in all cases by CT. Blood diseases with leukemia known before the onset of neurologic deficits and a history of traumatic brain injury or brain tumor were all excluded in above definitions.

Primitive reflexes examinations

The primitive reflex profile study involves the prospective sequential evaluation of primitive reflexes and the other aspects of motor functions of stroke patients. The examination was designed to score four primitive reflexes: the snout reflex, the jaw jerk, the glabellar sign, and the corneomandibular reflex. The snout reflex was elicited by a slight tap of the reflex hammer midline on the subject's upper lip. The cathode recording electrode was placed on the orbicularis oris muscle at 2 cm lateral to midline on upper lip and the reference electrode was placed on the mouth angle. The ground electrode was placed on the chin. Conduction latency and peak-to-peak amplitude of reflex response was measured by a Sapherie Primere EMG machine (Medelec, Surrey, UK). The glabellar reflex was produced by light tapping over the glabella with a reflex hammer by the examiner behind the patient. The cathode recording electrode was placed on the orbicularis oculi muscle midline on the subject's lower eyelid, whereas the reference electrode was placed on the lateral orbital angle. More than five repeated blinks elicited by repetitive stimuli were recorded. The jaw jerk was elicited by a tap of reflex hammer on the subject's mid-jaw. The paired recording electrodes were placed on the tempolaris muscle. For eliciting the corneomandibular reflex, the cornea was stimulated with a dry wad of cotton wool attached to a transducer switch (Figure 1) over the lower external quarter. The upper eyelid was held by the examiner to prevent interruption of the stimulus by the blinking which results from the corneal reflex. Paired recording electrodes were placed on the masseter muscle opposite to the stimulated cornea. Each reflex was stimulated at least 3 times, with an interval of 1-2 min between trials. The shortest conduction latency and the greatest amplitude of muscle action potential

were reocrded.

Test of cognition

The cognitive function of patients with stroke was assessed by the Mini-Mental State (MMS) examination[11]. The study being the search for a relationship between primitive reflexes and the severity of the dementia, patients were not assessed with a full neuropsychological battery. A full MMS score was 30 points, and lower scores signify increasing severity of cognitive impairment. Absence of dementia is defined by a score of 24 or more on the MMS examination.

FIM score measurement

Functional Independence Measure (FIM)[12], which is the 18-item, 7-level scale is used to assess the physical functioning and social cognition domains in stroke patients[13]. The FIM uses the level of assistance an individual needs for grading functional status from total independence (=7) to total assistance (=1). The scores may range from 18 to 126. The FIM assesses the level of disability regardless of the nature or extent of the underlying impairment. It is discipline-free, simple to use, reliable, uses an everyday terminology to describe disability, and is sensitive to the changes in the course of rehabilitation program.

Statistics

Statistical analysis of comparison of one group with another was performed with Student's t, chi-square and regression tests. The maximal level of significance was p=0.05.

RESULTS
Results of primitive reflexes

The conduction latencies, wave amplitude and persistence of jaw jerk, snout, glabellar and corneomandibular reflexes in the stroke patients and the normal controls were summaried in Table 1. The conduction latencies obtained in the stroke patients were not different from the results obtained in the controls, whereas the wave amplitude was higher in the stroke patients than in the controls (t-test, $p<0.05$). The results of snout reflex studies also showed a higher wave amplitude in the stroke patients than in the normal controls ($p<0.05$), but there is no significant difference in conduction latencies between the stroke patients and controls. In electrophysiologic study of glabellar reflexes, no difference has been observed between the results in conduction latencies and wave amplitude. Wave amplitude obtained in corneomandibular reflexes were found to be higher in stroke patients than in the controls ($p<0.05$). However, no definite difference of conduction latencies in both groups can be observed. The reflex persistence showed a significantly higher percentage in the stroke patients than in the controls in jaw jerk and snout reflexes.

The relation between the age and the presence of primitive reflexes in stroke patients is shown in Figure 2. The biserial correlation between age and the jaw jerk was 0.65 ($p<0.01$). A good correlation between the age and the snout reflex ($r=0.54$, $p<0.01$) can be seen. No correlation was observed between the age and the presence of an abnormal glabellar reflex ($r=0.32$, $p>0.1$) or between the age and the presence of corneomandibular reflex ($r=0.21$, $p>0.1$).

MMS and FIM scores

The mean age of 21 patients with infarctive stroke was 68.4 ± 3.3 years which is higher than the mean age of 17 patients with hemorrhagic stroke, 57.7 ± 4.1 years (p<0.05). Five infarctive stroke patients and eight hemorrhagic patients had MMS scores higher than 24 and were not categorized as dementia. The mean value of MMS scores obtained in infarctive strokes was 18.7±3.5 (range from 6 to 27) which is not significantly different from the value of 21.3±4.1 (range from 10 to 28) obtained in hemorrhagic strokes (p>0.1). Although a slight decrease of MMS score with age was noticed, no significant correlation can be made between the age and the MMS scores. In correlation study of MMS scores and primitive reflexes, a significant regression was found between the wave amplitude of snout reflexes and the MMS scores (r=-0.67, p<0.01, Figure 3). A positive correlation was also found between the wave amplitude of corneomandibular reflexes and the MMS scores (r=-0.53, p<0.05, Figure 4). The degree of abnormality in the MMS scores, however, did not show any correlation with the conduction latencies of primitive reflexes either in stroke patients or in the controls.

The results of FIM assessment in stroke patients are shown in Table 2. The mean value of FIM scores obtained in infarctive strokes was 63.5 ± 4.9 which is lower than the results obtained in hemorrhagic strokes, 91.2 ± 7.3 (p<0.05). There is a significant difference in FIM scores between the groups of infarction and hemorrhage (t-test, p<0.05). The persistence of primitive reflexes was correlated with the degree of abnormalities on the FIM scores. From the results of electrophysiological study of primitive reflexes, the wave amplitude of snout reflex and jaw jerk can be well correlated with the FIM scores (r=

-5.1, p<0.05; r= -4.4, p<0.05; respectively). The FIM scores were found to have no correlation with the conduction latencies in four kinds of primitive reflexes studies.

DISCUSSION

High incidences of primitive reflexes have been reported in association with a variety of diseases of the central nervous system, including Parkinsonism, advanced organic dementias, diffuse encephalopathies, normotensive hydrocephalus, post-traumatic states, neoplasms, and cerebral degenerations.[14] Although the anatomical substrates of these reflexes are unknown, Paulson and his colleagues[15], through a study of demented patients, concluded that primitive reflexes are associated with diffuse, bilateral, irreversible disease of the central nervous system and are nearly always attributable to diffused cortical atrophy. Jenkyn et al.[16] suggested that the primitive reflexes were mainly associated with cognitive dysfunction.

Since stroke patients make up the largest category of patients seen in rehabilitation hospitals, a major consideration in the selection of such patients for treatments directed at regaining lost functions or learning new activities should be made and the extent to which these individuals are able to profit from the treatment. Traditionally, the neurological examinations are used to establish lesion site and diagnosis, and to associate examination findings with particular function. Various studies on primitive reflexes are that the values given for the prevalence and incidence of these signs vary among the publications. Most of studies in primitive reflexes describe the presence or absence of the responses and shows the diversity in the assessments in scoring. The

type or intensity of reflex stimulation is often not standardized in the experimental observations, and rarely standardized in the clinical ones. Furthermore, most of the responses are complex and the isolation of individual components is difficult or arbitrary. Present study of primitive reflexes with the electrophysiological methods, makes it a quantitative measurement, would be useful in the evaluation of stroke patients.

In the present study of four primitive reflexes, jaw jerk, snout reflex and glabellar blink reflexes were techniquely easy to perform with stimulation and recording. However, the examination of corneomandibular reflex needs more cooperation from the patient. A constant touch pressure to the cornea by a cotton wad is required to elicit the switch on the transducer and to induce the trigger of the test. The discomfort of test with irritation of eye results in some difficulty in procession of the test. This limitation may affect the consistency of the reflex test. This may be one of the possible reasons for the lower persistence of corneomandibular reflexes (26%) as compared to the values of jaw jerk (74%) and snout reflexes (63%), observed in the present study.

Our results from electrophysiological study of primitive reflexes show that the reflex wave amplitudes are higher in stroke patients than in controls, whereas the reflex conduction latencies in stroke patients are same as in controls. This result demonstrates that the conduction time of reflex arc in sensori-motor (trigemino-facial) systems is same both in stroke patients and in controls. However, the reflex responding neurons with no central control are more excitable in stroke patients than in normal controls. By the analysis of clinical findings of stroke patients, we found that the appeared persistence of primitive reflexes increase with the duration and severity of stroke. But the appearance of primitive

reflexes was not different in stroke types for example, in hemorrhage or infarction. The primitive reflexes cannot be correlated well with the localization of brain lesion. These findings suggest that the primitive reflexes do not have great localizing value, instead it is diffused and widespread dysfunction of the hemispheres.

A regression was found between the reflex wave amplitude and MMS scores , by correlating MMS scores and primitive reflexes obtained in the present study. This finding demonstrates that the primitive reflexes are associated with cognitive dysfunction in stroke patients. Cognitive dysfunction in stroke patients reflects a disinhibition of cortical neurons and a progressive release of brain structures from cortical inhibition because of diffused cortical atrophy. Lower center neurons were frequently excited and lead to the greater amplitude of the reflex response in electrophysiological study. The FIM score measurement has the advantage of including measures of cognitive function, communication, and social functioning. From the present study, a correlation can be made between the FIM scores and the wave amplitude of primitive reflexes in stroke patients. The relationship between the MMS and FIM scores is compatible with the view that these reflexes are a sign of diffuse cerebral dysfunction, rather than a symptom of a distinct neurological disease.

In conclusion, our measurement of primitive reflexes with the help of electrophysiological assessments may provide an objective and quantitative way in the diagnosis of disinhibition syndrome in stroke. Cognitive impairment in relation with the disabilities in daily living was compatible with the appeared persistence of primitive reflexes. This objective study of primitive reflexes may be used as a tool in evaluation of outcome in stroke rehabilitation.

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Table 1- Conduction latency, wave amplitude and persistence of primitive reflexes in stroke patients and controls. (mean±SEM)

	number of subject	latency (ms)	Amplitude (µV)	persistence (%)
Jaw Jerk				
stroke patient	38	6.88 ± 1.05	257 ± 142	$74\,\beta$
normal control	26	7.04 ± 0.87	126 ± 113	$19\,\beta$
Snout Reflex				
stroke patient	38	11.2 ± 0.6	$633 \pm 175^{\#}$	$63*$
normal control	26	10.8 ± 1.1	$146 \pm 87^{\#}$	$16*$
Glabellar Reflex				
stroke patient	38	7.3 ± 1.2	315 ± 114	$39@$
normal control	26	8.0 ± 1.5	264 ± 89	$23@$
Corneomandibular reflex				
stroke patient	38	12.7 ± 3.5	$851 \pm 126\,\alpha$	$26\,\S$
normal control	26	10.8 ± 5.2	$253 \pm 117\,\alpha$	$11\,\S$

#: $p<0.01$, α : $p<0.05$, by Student's t test

β, *: $p<0.05$; @, § : $p>0.1$, by chi-square test, respectively

Table 2- Basic information, mini-mental state (MMS) and functional independence measure (FIM) scores in stroke patients (mean±SEM).

	no. of patient	age (year)	MMS score	FIM score
Stroke				
infarction	21	68.4±3.3	18.7±3.5*	63.5±4.9#
hemorrhage	17	57.7±4.1	21.3±4.1*	91.2±7.3#

*: p>0.1, #: p<0.05 by Student's t test, respectively

Table 3- Conduction latency, wave amplitude and persistence of palmomental
reflex obtained in stroke patients and normal controls (mean±1SD)

	number	latency (ms)	amplitude (µV)	persistence (%)
Stroke patient	23	24.6 ± 7.9#	125 ± 82*	75@
Normal control	16	17.2 ± 4.5#	70 ± 53*	25@

#, *: P<0.05, respectively by Student's t test
@ P<0.01 by chi-square test

LEGENDS FOR ILLUSTRATIONS

1. The stimulator for corneomandibular reflex examination.

2. The relation between the age and the presence of primitive reflexes in stroke patients

3. The relation between the wave amplitude of snout reflexes and the mini-mental scores (MMS) in stroke patients.

4. The relation between the wave amplitude of corneomandibular reflexes and the MMS scores in stroke patients.
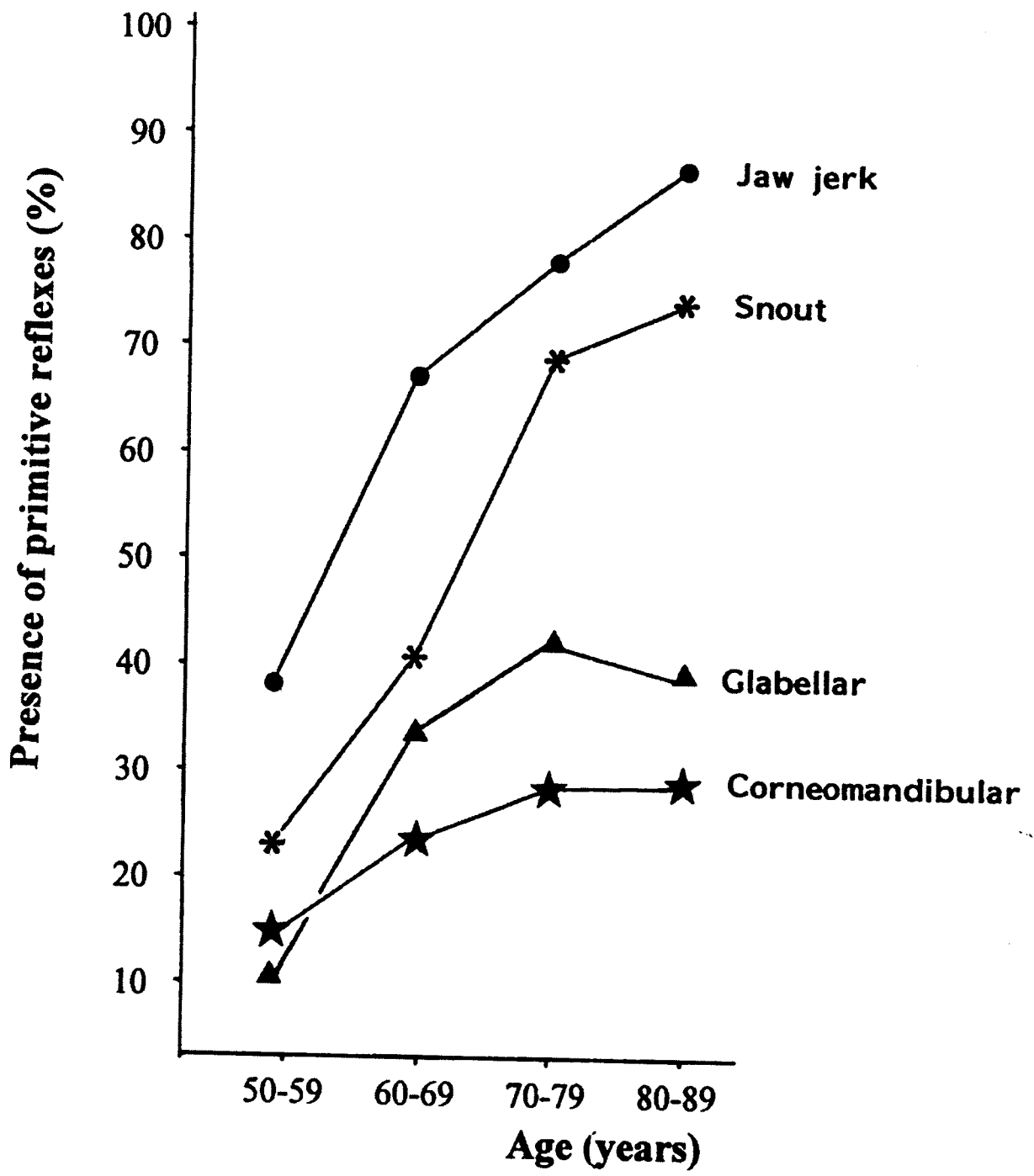
FUNCTIONAL INDEPENDENCE MEASURE (FIM)

Levels: Complete independence (Timely, Safely) , no helper-------------- 7

Modified independence (Device) , no helper----------------------6

Modified dependence, helper

    Supervision---5

    Minimal assist--4

    Moderate assist--3

Complete independence

    Maximal assist--2

    Total assist --1

|	
Self Care 1. Eating	_____
2. Grooming	_____
3. Bathing	_____
4. Dressing (upper body)	_____
5. Dressing (lower body)	_____
6. Toileting	_____
Sphincter Control 1.Bladder management	_____
2. Bowel management	_____
Mobility / Transfer 1. Bed, Chair, Wheelchair	_____
2. Toilet	_____
3. Tub, Shower	_____
Locomotion 1. Walk/Wheelchair	_____
2. Stairs	_____
Communication 1. Comprehension	_____
2. Expression	_____
Social cognition 1.Social interaction	_____
2.Problem solving	_____
3.Memory	_____

TOTAL FIM SCORE   _____

Switch

Touch plate

Plug to transducer
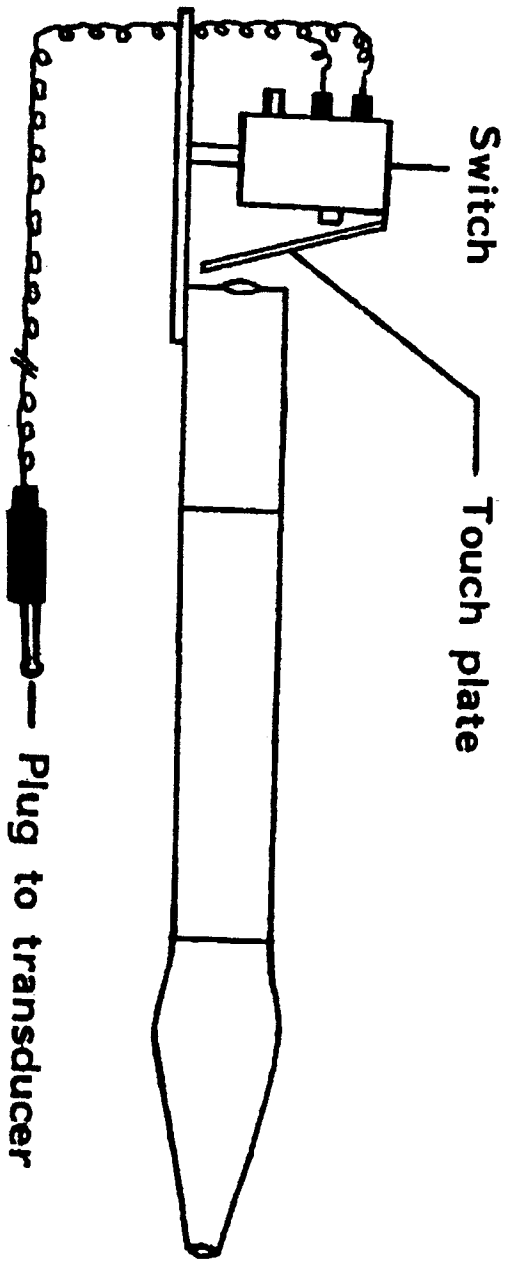
Wad

Amplitude of Snout Reflex (μV)

r = −0.67

MMS
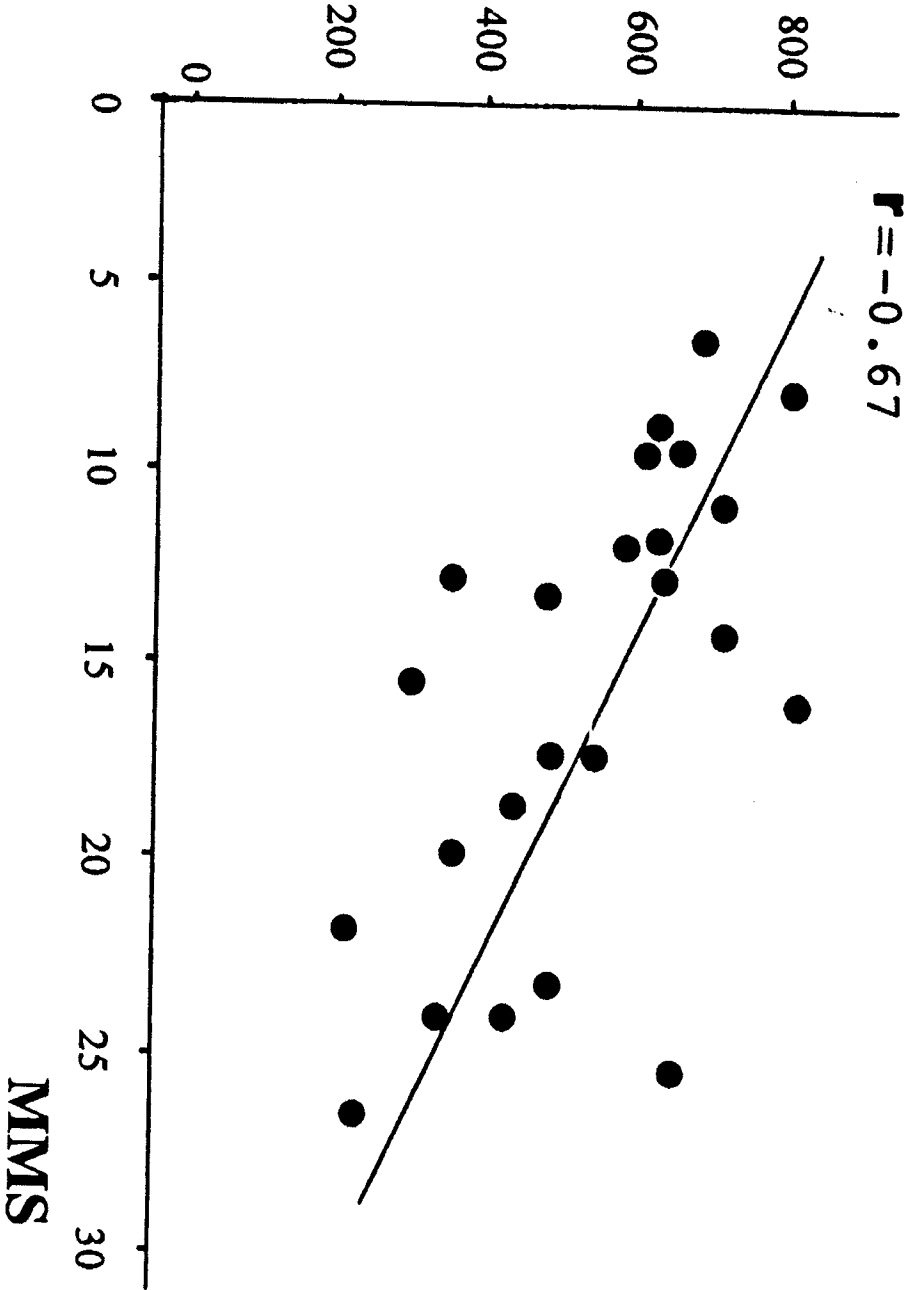
Correlation of MMS scores and amplitudes of CMR

Amplitudes of CMR (uV)

MMS scores

r = -0.53

y = -13.537x + 622.83