A DOUBLE BLIND STUDY TO EVALUATE THE EFFICACY OF DISTRIBUTION OF F- LATENCY (DFL) IN THE DETECTION OF CERVICAL RADICULOPATHY AND MYELOPATHY

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ABSTRACT

Distribution of F-Latency (DFL) is a new parameter in peripheral nerve conduction measurement and an important application of this new technique is the detection of Cervical Radiculopathy and Myelopathy (CRM) at an early stage through an evaluation of its pattern. Typically a single sharp peak corresponds to normalcy while double peak or a broad peak represents pathology. The current study is an exercise in validating DFL as a screening tool for CRM by comparing the data obtained from an extended pool of subjects (56 median nerves of 28 persons) against corresponding MRI findings through a double blind study. Subject selection was done randomly A 1.5 Tesla MRI scanner and a home built Computerised EMG equipment were used for this study. Analysis of data gave a correct prediction or efficacy of 75%, sensitivity of 77% and specificity of 50%. The present study establishes DFL on a stronger footing for assessment of cervical radiculopathy and myelopathy, whether due to spinal cord or nerve root compression. In combination with conventional simple clinical tests, DFL is expected to give better information for diagnosis of CRM. Being a non-invasive technique requiring virtually zero expenditure in consumables, it promises greater access to patients, and could be used for extensive prevalence study, which cannot be performed using MRI. The capability of DFL in detecting subclinical stages of CRM holds a promise as an awareness development tool alongside screening for neuropathy.

Keywords: Distribution of F-Latency, Radiculopathy, Myelopathy, Spondylosis, Neuropathy, EMG

INTRODUCTION

Distribution of F-Latency (DFL) obtained from multiple F-responses is a new parameter in peripheral nerve conduction measurement initiated by our extended group in Dhaka University which has been established to give a distribution of Conduction Velocity (DCV) of motor nerve fibres in a peripheral nerve trunk as its approximate mirror image (Rabbani et al 2007). To determine DCV experimentally an alternative method and its few variations exist which are based on collisions of two nerve action potentials generated through two stimulators with varying time delay. However, these methods (Hopf 1962, Ingram et al 1987, Harayama et al 1991) are complex and conceptually prone to error (Rabbani et al 2007).

Through earlier work of our extended group it was indicated that DFL obtained from the median nerve has a single peak for normal subjects while a double or a triple peak is demonstrated for subjects having cervical spondylosis (Alam and Rabbani 2010). Hypotheses were put forward (Rabbani 2011) in terms of segmental lesions in a nerve trunk, caused by both radiculopathy (compression of nerve roots) and myelopathy (compression of spinal cord). Broad peaks were hypothesized to represent early cervical spondylosis. Of course, partial nerve injuries also appeared to cause double peaks through clinical experience of our extended group (Rabbani 2011), therefore, in the assessment of cervical radiculopathy and myelopathy (CRM), cases with injuries near the nerve were avoided.

Extensive laboratory and clinical testing of DFL has firmly established that the test results are very consistent and repeatable on the same subjects (Rabbani et al 2007). This indicates that it is potentially very suitable as a clinical test. It has been possible to detect subclinical cases of cervical radiculopathy and myelopathy where the patients did not have any complain or symptoms to suggest the clinical condition but after a suggestion from DFL, X-ray or MRI revealed the presence of neuropathy (Hossain et al 2011). All these findings indicate that DFL could be very useful as a screening test for CRM, for subjects without any history of nerve injury.

In the diagnosis of CRM, MRI is the standard investigation carried out. However, DFL is much less expensive and easier to perform than MRI. So we took up the present work in order to establish the efficacy of DFL as a screening test for CRM on a firmer footing. In order to do so in an unbiased manner we have attempted to compare and correlate DFL obtained from the Median nerve of many subjects to MRI findings of the corresponding cervical region in a double blind experiment. We also plan to assess the cost effectiveness of this technique through predictive analyses using binary classification methods, in terms of sensitivity and specificity. The results will indicate whether DFL may be used as a screening test for cervical radiculopathy and myelopathy.

METHODS

The aim of the present work was to study the effectiveness of DFL for diagnosis or screening of CRM. In the diagnosis of CRM, MRI is the standard investigation carried out. So we decided to carry out a double blind trial involving both DFL and MRI, where the findings of DFL will be evaluated against the findings of MRI, considered as the 'Gold Standard' in these measurements.

These investigations were carried out on both symptomatic and asymptomatic subjects. The Radiologist conducting MRI was not informed of the DFL findings. Also the investigator assessing the DFLs was unaware of the MRI results. This was done to keep the trial double blind so that there is minimum bias.

A pool of 28 volunteers was chosen to take part in the investigation. The selection process was random. Oral consent was taken from the subjects prior to testing, and it was noted whether the patient had any history of cervical pain or prior diagnosis of cervical radiculopathy/ myelopathy. First they were subjected to MRI test at the Square hospital and later tested for DFL at the Trauma Center, both located in Dhaka, the latter using a nerve conduction equipment developed locally by our extended group earlier in 1988 with the support of scientists from UK (Rabbani et al 1989). Clinical neurologic evaluation of the subjects was not done.

The F – responses of individual subjects were taken from each hand by stimulating the Median nerve at the wrist and the recording the evoked response from the thenar muscle of the palm, at the base of the thumb (APB muscle).

The Median nerve was stimulated in four blocks of ten stimulations each for a total of 40 stimulations. The F- responses (which exceeded 30 in all cases) were recorded and then sorted into latency bins of 2ms duration (bin width). Then a distribution of F- latency (DFL) was plotted as a frequency polygon.

The DFL results were evaluated according to predetermined criteria to indicate a positive CRM as follows:

i. if the DFL has two or three distinct peaks,
ii. if non-zero frequencies were found with a separation of more than 4ms from the highest frequency value (at a gap of two bin widths),
iii. if the DFL has a clear broad peak,

iv. if the frequency of the adjacent bin was more than one third as high as the highest frequency

The last condition was put forward by a previous work carried out in Singapore and Dhaka (Rabbani et al 2014)

MRI investigation of the cervical spine was done of each subject using a GE Signa1.5 Tesla machine supplied by General Electric Corp at the Square Hospital, Dhaka.

Two sequences were taken (Sagittal and Axial) and the protocols were as follows

i. T2 (Sagittal) T(R) – 3060 ms, T(E)- 116.5 ms
ii. T2 (Axial) T(R)- 500ms, T(E)- 15.2 ms

The MRI findings were evaluated for nerve root compression because of osteophytes or disc herniation and spinal cord compression because of disc herniation at the level of the cervical spine.

Since the APB muscle is supplied by nerve roots C7, C8 and T1 (Alam and Rabbani 2010), root compression at these levels only were considered as positive for radiculopathy. These are the locations for root compression of our interest.

It was hypothesized in the earlier work that compression of the spinal cord at a position in the conduction pathway of a descending nerve would lead to atrophy or degeneration of the peripheral motor neurons with cell bodies in the lower vertebral levels with which the descending nerve synapses. So if the anterior horn cells of a motor nerve was degenerated in this way it would also show up as broadened peak in DFL (Rabbani et al 2010). Therefore, spinal cord compression due to disc herniation at slightly higher levels, C4/5, C5/6, C6/7 and C7/T1 were considered as positive for myelopathy. Again, these are the locations for spinal cord compression of our interest.

To rate the degree of compression as indicated by the MRI scan the severity of the defect was indicated by the number of stars (*), single star (*) indicating mild abnormality, double star (**) indicating moderate abnormality and triple star (***) indicating severe abnormality. The absence of star indicates normal condition (negative for CRM).

The DFL and MRI findings were evaluated separately and only brought together for comparison at the end of the investigation to ensure the double blind nature of the study. Here the MRI result was assumed standard against which the DFL outcomes were compared. To assess the cost effectiveness of this technique through predictive analyses using binary classification methods, in terms of sensitivity and specificity, the DFL results were grouped as i) True positive (TP), ii) False positive (FP), iii) True negative (TN) and iv) False negative (FN). From the above analysis the prediction capability of DFL were analysed in terms of predictive values, Correctly Predicted percentage (Efficacy), Wrongly predicted percentage, Sensitivity and Specificity.

RESULTS

Presence or absence of CRM in all the subjects as indicated by DFL, based on our defined conditions in the previous chapter, were collected. Each subject has two nerves on two sides under study. Thus for 28 subjects studied, the number of nerves is twice, i.e., 56. The diagnosis is given in terms of Yes (Y) or No (N), indicating presence or absence of CRM respectively. A few representative samples of data, including their DFL, are presented in Table 1. The abbreviations used related to the patterns of DFL are defined in the table caption. The corresponding MRI findings of the same pool of subjects are given in Table 2. Again, some details on the radiological findings on the lesions of interest are given through abbreviations, defined in a note below the table. This table also has a sub-table showing

our interest, either in Myelopathy (Cord Compression) or in Radiculopathy (Root Compression), or in both, at particular vertebral levels as mentioned before. As mentioned in the previous chapter, at each level the severity of the defect was indicated by the number of stars (*).

Table 1: Sample of DFL findings for CRM
[Abbreviations are: BP - Broad peak, DP - Double peak, SP - Single peak]

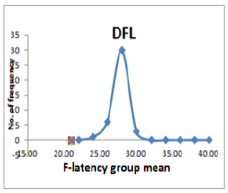
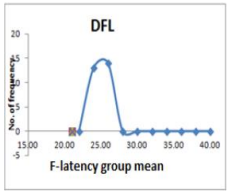
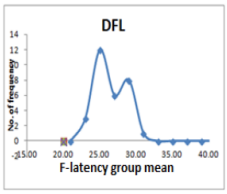
Subject No	Age	Sex	DFL		
			Pattern	Findings	Diagnosis
Subject 1	22	F		SP	N
Subject 2	25	M		BP	Y
Subject 3	25	M		DP	Y

Table 2: MRI findings for CRM
(Please see notes below)

Subject No	MRI Findings				Diagnosis
	Spinal Level	Description of findings	Compression		
			Cord	Root	
Subject 1	C3-4	DH, O, TSI, NFN	**	*	Yes
	C4-5	DH, O, TSI, NFN	**	*	
	C5-6	DH, O, TSI, NFN	**	**	
	C6-7	DH, O, TSI, NFN	**	**	
Subject 2	C3-4	DH, TSI	*		Yes
	C4-5	AT, DB, O, TSI, NFN	**	*	
	C5-6	No findings			
	C6-7	DB, TSI	*		
Subject 3	C3-4	AT, TSI	**		No
	C4-5	No findings			
	C5-6	No findings			
	C6-7	No findings			

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Note 1: We are interested in the compression of the median nerve affecting the cervical roots supplying the thenar muscle (namely C7, C8 and T1). So for compression in the nerve root we note any problems at the levels C5-C6, C6-C7 and C7-T1. Whereas for compression of spinal cord we examine the levels C4-C5, C5-C6 and C6-C7. This is summarized in the sub-table on the right.

Compression	
Cord	Root
C4-5	C5-6
C5-6	C6-7
C6-7	C7-T1

Note 2: Abbreviations are: AD - abutting disk, AT - annular tear, CC - cord compression, CI - cord Indentation, DB - disk bulge, DE - disk extrusion, DH - disc herniation, DHR-disc height reduction, FaH - facet hypertrophy, FlH - flavum hypertrophy, FDH – foraminal disc herniation, FO - foraminal osteophytosis, NFN - neural foraminal narrowing, NRI- nerve root impingement, O - osteophytosis, RE - right eccentricity, TSE - thecal sac effecement, TSI – Thecal sac indentation. A single '*' indicates minimal or presence of the particular feature, double '**' and triple '***' represents increased severity. The absence of star indicates normal condition.

As mentioned in the previous chapter the present work is specifically addressed to the measurement on the APB muscle which is supplied by nerve roots from C7, C8 and T1 (corresponding vertebral spaces: C6-7, C7-T1, T1-T2). Therefore, radiculopathy in these three roots were of interest. Again, Myelopathy at immediate one or two levels above were of interest (corresponding vertebral spaces: C4-5, C5-6, C6-7, C7-T1). Abnormal DFL is expected to occur for both these types of neuropathy as mentioned before.

The MRI and DFL data were combined into a single table (Table-3).

Table 3: Comparing MRI and DFL diagnosis for CRM

Subject No	MRI Diagnosis	DFL Diagnosis
1	Y	Y
2	Y	Y
3	Y	Y
4	Y	Y
5	Y	N
6	Y	Y
7	Y	N
8	Y	Y
9	Y	Y
10	Y	Y
11	Y	Y
12	Y	Y
13	Y	Y
14	Y	Y
15	Y	Y
16	Y	Y
17	Y	Y
18	Y	Y
19	Y	Y
20	Y	Y
21	Y	Y
22	Y	Y
23	Y	Y
24	Y	Y
25	Y	Y
26	N	Y
27	Y	Y
28	Y	N

Subject No	MRI Diagnosis	DFL Diagnosis
29	Y	Y
30	Y	Y
31	Y	Y
32	Y	Y
33	Y	Y
34	Y	Y
35	Y	Y
36	Y	N
37	N	N
38	Y	Y
39	Y	N
40	Y	N
41	Y	N
42	Y	Y
43	Y	Y
44	Y	Y
45	Y	N
46	Y	Y
47	Y	Y
48	Y	N
49	Y	Y
50	Y	N
51	Y	Y
52	Y	N
53	N	N
54	N	Y
55	Y	Y
56	Y	N

An analysis of the DFL and MRI results were performed to give the counts for True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) events which were subsequently used to obtain figures for correct prediction, wrong prediction, Sensitivity and Specificity. The corresponding results of these analyses are given in Table 4. These results will indicate the utility of the new test method, DFL, in diagnosis or screening of CRM which are further discussed in the next chapter.

Table 4: Efficacy of DFL findings

(Total 56 Median nerves tested)

True +ve	True - ve	False +ve	False -ve	**Correctly Predicted (Efficacy) %**	Wrongly Predicted %	Sensitivity %	Specificity %
40	2	2	12	**75**	25	77	50†

†Number of true negative cases are not enough

DISCUSSION

The work on DFL (which is a statistical frequency distribution of F-latencies from multiple F-responses) and the exploration of its benefit in the diagnosis of cervical spondylosis has progressed through several steps. First came the conceptual realization that DFL was an approximate mirror image of DCV of nerve fibers which can be electrically stimulated. Secondly, a human study was conducted to establish that DFL was a repeatable thus a physiological parameter which returns consistently similar results upon repeated testing of the same individual nerve which in turn verified the above concept. The third step was the establishment that it was sensitive to nerve compression due to any cause, resulting in a delay shift of the DFL. During this study there was a fortuitous observation that among the subjects tested, the ones returning a broad, double or triple peak of DFL were diagnosed cases of cervical spondylosis, or alternately suffering from neck pain while normal subjects demonstrated a single peak. This observation brought about a question as to whether DFL was correlated to cervical spondylosis. A set of hypotheses invoking the segmental compression or degeneration of nerves were formulated based on physiological and statistical arguments to explain the observations. The fourth study attempted to verify the hypotheses through a correlation between the DFL and X-ray findings (with a few MRI) of known cases of cervical spondylosis. This finding was further confirmed through comparison of DFL and MRI in a study conducted at Singapore General Hospital on patients with radiculopathy.

One of the important outcomes of the Singapore work was the definition of a broad peak of DFL. Earlier a clear broad peak was defined where non-zero frequency exists at 4 ms difference from the position of the peak of DFL (considering a bin size of 2 ms for the frequency distribution). However, this work helped in redefining the broad peak to include shapes that were only marginally broad. Through a comparison with the MRI findings a rule of thumb was made to define such a broad peak; it will be termed a broad peak if an adjacent (at a separation of 2 ms) frequency to a peak is more than one third that at the peak. Thus the new definition of broad peak (though still arbitrary) has improved

the correlation with MRI findings. The Singapore study was a valuable learning experience and the redefined criteria for broad peak thus obtained, was used in the analysis of the current study.

The current trial tries to establish the cost effectiveness of using DFL as an alternative to MRI in the detection of CRM through a double blind study. MRI is so far considered the gold standard in the diagnosis of CRM, but it is expensive, time consuming, and the evaluation is qualitative rather than quantitative. Besides, it is also dependent on the expertise and experience of the investigator. DFL on the other hand is a functional and objective test, and uses equipment that can be made at a low cost, with almost zero consumable expense. Furthermore, MRI is not portable and is not widely available while equipment to measure DFL (conventional EMG equipment) can be made portable. Therefore if the efficacy of DFL in the detection of CRM is borne out through the present work, this could provide an important milestone in neuromedicine.

In the current study the patient selection was random. They were chosen irrespective of clinical history but effort was there to keep adequate number of subjects in the two age groups considered. The stimulation interval used to obtain the F responses was set at one second to ensure that the refractory period of the physical mechanisms involved was much less than the time gap between two stimulations. Since DFL requires that each event related to a stimulation is random therefore, stimulation induced physiological processes are required to end much before the next stimulus, thus making each event independent of history.

The centre that performed MRI in the present work does not image the T1 vertebral section routinely. Because of this oversight, information of the contribution of radiculopathy at this level is missing from the present MRI findings. This definitely could affect the results, strictly speaking. However, it is reported that the prevalence of cervical myelopathy is much higher than that of cervical radiculopathy (Young 2000), so the results will be affected slightly through this omission. The results show a correct prediction score of 75% This indicates that DFL is a very sensitive tool for identification of CRM. In fact in many of the cases, the person did not have any complain, but DFL indicated abnormality. That means DFL can detect CRM even in the subclinical phase increasing its utility in clinical management.

In terms of the details, the sensitivity and specificity values were 77% and 50% respectively . The specificity is low because there were not too many cases without CRM, an important point revealed by this work. However, the efficacy is the parameter that we would like to stress more in this study.

The efficacy of 75% is good for a new, simple and low cost diagnostic method. The present study shows that DFL is well correlated with MRI with reasonably high efficacy. So it is very promising as a screening tool.

However, taking MRI as a gold standard is also questionable since the resolution of the images may put a limitation on the assessment of compression. In many cases Thecal sac indentation was rather blunt and it was not clear whether it affected one side more than the other. On the other hand, DFL gives clear and distinct side discrimination. This could have affected the results of the present study as well. Therefore, the low values of specificity obtained in this work could have been due to this limitation of MRI. Perhaps studies with an MRI with greater magnetic field strength may give a better answer. In fact DFL is a very sensitive technique as it can detect subclinical CRM.

The capability of DFL in detecting subclinical stages of CRM holds a promise as an awareness development tool alongside screening for prevalence of neuropathy. Those individuals who are diagnosed as positive for CRM and are still asymptomatic could be persuaded to make changes of lifestyle to lessen the chance of progression of their health condition.

The present study can be extended further to include the examination of Lumbosacral spondylotic neuropathy by evaluating the Tibial and Common Peroneal nerves which have already shown similar features. Other neurologic conditions such as Gullian Barre syndrome, diabetic and uremic neuropathy etc, could also be explored with this technique.

Presently DFL is limited in that it cannot determine the location and type of lesion (whether radiculopathy, myelopathy, trauma or other lesions) involved. Further work has already been taken up to differentiate radiculopathy from myelopathy using DFL in conjunction with the M-response, which is acquired as a standard procedure in nerve conduction measurements. Besides, to identify the levels of the lesion, it is being planned to use DFL together with other nerve conduction parameters and standard clinical examinations. It is expected that a combination of DFL and simple clinical investigations may give a test with diagnostic value similar to that of MRI, particularly in the diagnosis of radiculopathy and myelopathy.

The current study along with past clinical experience in our laboratory indicates that there is a high prevalence of undiagnosed or early stage cervical radiculopathy/myelopathy. No extensive prevalence data for CRM are available in the literature; the limited availability and the high cost of MRI equipment may be the cause behind. Most reports deal with cases that come to a hospital for treatment only, which is of no use for a general prevalence study. A large population will not come to a hospital although they may have CRM but to a tolerable level. Most studies suggest that cervical myelopathy is the most common spinal cord disorder in individuals aged 55 and older in the US (Young 2000). Holt and Yates (1966) reported that the prevalence of cervical spondylotic myelopathy is 50% in men and 33% in women by 60 years of age.

The present study establishes DFL on a stronger footing for assessment of cervical radiculopathy/ myelopathy, whether due to spinal cord or nerve root compression. With further development, the performance is expected to improve making it more effective. Dedicated portable equipment giving M-response and DFL on a computer monitor can be made at reasonably low cost, and our extended group at Dhaka is already working on this. Being a non-invasive technique requiring virtually zero expenditure in consumables, it promises greater access to patients, and could be used for extensive prevalence study. Large screening studies should be conducted using DFL to further explore the finding of the high incidence of CRM in the younger population as well as in the aged.

In conclusion, DFL could become a screening tool for early detection of cervical spondylosis, and used as an awareness building tool of choice. The present work has been successful in establishing the new technique of DFL in the detection of cervical radiculopathy/ myelopathy with greater confidence. Thus this study could be a stepping stone for its global acceptance.

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