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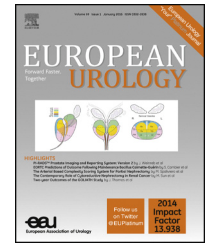

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Surgery in Motion

Establishment of Novel Intraoperative Monitoring and Mapping Method for the Cavernous Nerve During Robot-assisted Radical Prostatectomy: Results of the Phase I/II, First-in-human, Feasibility Study

Won Hoon Song [a,b], *Ju Hyun Park* [a,c], *Bum Sik Tae* [a,d], *Sung-Min Kim* [e], *Min Hur* [f], *Jeong-Hwa Seo* [f], *Ja Hyeon Ku* [a], *Cheol Kwak* [a], *Hyeon Hoe Kim* [a], *Keewon Kim* [g,*], *Chang Wook Jeong* [a,*]

[a] *Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea;* [b] *Department of Urology, Pusan National University Yangsan Hospital, Pusan National University Colleage of Medicine, Yangsan, Republic of Korea;* [c] *Department of Urology, Seoul National University Boramae Medical Center, Seoul, Republic of Korea;* [d] *Department of Urology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea;* [e] *Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea;* [f] *Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea;* [g] *Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea*

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Abstract

Background: Potency preservation often does not meet expectation despite nerve-sparing prostatectomy.
Objective: To set the protocol for intraoperative cavernous nerve monitoring and mapping during robot-assisted radical prostatectomy (RARP), and to evaluate its safety and clinical feasibility.
Design, setting, and participants: A prospective phase I/II, feasibility study was performed. A total of 30 patients with prostate cancer who underwent RARP at a high-volume tertiary academic hospital were enrolled.
Surgical procedure: Pudendal somatosensory evoked potential, bulbocavernosus reflex, spontaneous corpus cavernosum electromyography (CC-EMG), median nerve stimulation evoked CC-EMG, and neurovascular bundle (NVB)-triggered CC-EMG with various stimulation protocols were assessed during conventional RARP under total intravenous anesthesia with controlled muscle relaxation.
Measurements: The primary endpoint was the completion rate of planned surgery and assessment. Adverse events, and erectile and urinary functions were evaluated within 1 yr. CC-EMGs were graded and correlated with functional outcomes.
Results and limitations: The completion rate was 100%. Only one patient experienced adverse events, which were not related to study intervention. Grades of CC-EMGs including NVB-triggered CC-EMG before prostate removal were associated with baseline five-item International Index of Erectile Function (IIEF-5) score (grades 0–1, 4.6 ± 2.7; grade 2, 13.2 ± 6.8; grades 3–4, 16.6 ± 5.9; $p = 0.003$). Furthermore, grades of CC-EMGs including NVB-triggered CC-EMG after prostate removal were significantly associated

* Corresponding authors. Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. Tel. +82 2 2072 3899; Fax: +82 2 742 466 (C.W. Jeong). Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. Tel. +82 2 2072 2619; Fax: +82 2 743 7473 (K. Kim).
E-mail addresses: keewonkimm.d@gmail.com (K. Kim), drboss@snu.ac.kr (C.W. Jeong).

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with potency recovery (grade 0, 12.5%; grade 1, 0%; grade 2, 33.3%; grades 3–4, 100% at 12 mo; $p = 0.005$) and postoperative IIEF-5 scores at all evaluation time points (grades 0–1, 2.6 ± 2.8; grade 2, 4.3 ± 5.8; grades 3–4, 15.7 ± 11.0 at 12 mo; $p = 0.003$).
Conclusions: We successfully established the protocol for safe intraoperative cavernous nerve monitoring and mapping using CC-EMG during RARP. Its grades were well correlated with erectile function.
Patient summary: In this first-in-human feasibility study, we successfully established the protocol for safe intraoperative cavernous nerve monitoring and mapping method during robot-assisted radical prostatectomy. The results were significantly associated with erectile function. Evaluation of clinical efficacy to preserve potency seems worthy of further optimization and investigation in confirmatory clinical trials.

1. Introduction

Radical prostatectomy (RP) is the most common initial treatment for localized prostate cancer (PCa) [1]. However, it is associated with significant post-treatment sexual and urinary dysfunction [2,3], consequences that may be magnified by prolonged disease course [4]. Despite advancement in surgical techniques in the robotic surgery era, erectile dysfunction remains the most prominent functional complication even after nerve-sparing RP [5–7]. As the contemporary concept of neurovascular bundle (NVB)-sparing technique has been developed based on an imaginary surgical plane along with an invisible cavernous nerve [5], a more precise cavernous nerve-preserving technique is strongly required beyond the current surgical paradigm. To achieve this progress, a better understanding of neurophysiology related to erection and a quantitatively measurable technique during surgery will be the first step.

A few attempts had been made before [8–12]. However, not all were successful because indirect secondary response was measured in previous studies, which had lower sensitivity and specificity [9,13]. Corpus cavernosum electromyography (CC-EMG), or the direct measurement of neuroelectrical activity in the corpus cavernosum, has attracted considerable attention in this respect. Since the first report by Wagner et al in 1989 [14], this technique had evolved as a neurologic test for the differential diagnosis of erectile dysfunction [15–17]. Nonetheless, CC-EMG in its original application has not been accepted widely. However, we showed the potential of CC-EMG in its new application—that is, intraoperative nerve monitoring and mapping (IONM) during RP—because we can directly stimulate the cavernous nerve and the integrity of innervation may dramatically change.

Thus, we performed the Monitoring and Mapping of Erectile Nerve during Robot-Assisted Radical Prostatectomy (MMEN) study (NCT0257427). This prospective first-in-human, phase I/II study aimed to better understand the neurophysiology of erection using comprehensive neurologic tests including CC-EMG, to set the best protocol for intraoperative cavernous nerve monitoring and mapping, and to evaluate its safety and clinical feasibility. The specific objective of this feasibility study was to evaluate (1) whether CC-EMGs are recorded in the operative setting, (2) whether CC-EMGs are similar between potent and impotent men, (3) how CC-EMGs change after NVB-sparing or NVB–non-sparing procedures, and (4) whether the signal can be quantified.

2. Patients and methods

2.1. Ethics statement

The study was approved by the institutional review board of Seoul National University Hospital, Seoul, Republic of Korea (H-1504-070-664). Written informed consent was obtained from all patients.

2.2. Patients and surgery

Male patients aged 19–80 yr who (1) had pathologically proven PCa (≤cT3a), (2) underwent robot-assisted RP (RARP), (3) had Eastern Cooperative Oncology Group performance status of 0 or 1, and (4) could read and agree with the contents of the informed consent form were included in the study. Patients who received prior treatment for PCa or radiation therapy/surgery in the pelvic cavity or refused to participate in the study were excluded. As this study is the first-in-human, feasibility study, we did not limit the eligibility criteria to preoperatively potent men or NVB-sparing cases to broaden our knowledge.

A total of 30 patients at a tertiary referral hospital were prospectively enrolled from July 2015 to March 2017. All patients underwent conventional six-port transperitoneal RARP in antegrade fashion with minor modification [18,19]. The degree of NVB sparing was determined through shared decision making based on clinical information, results of nomograms to predict pathologic stage [20] and recurrence-free probability [21], and multiparametric prostate magnetic resonance imaging. NVB dissection was performed using the usual athermal and traction-free technique. Hem-o-lok or metal clips were selectively used to control the pedicle and small vessels. If needed, bleeding vessels in the neurovascular bundle and around the apex were stitched. Van Velthoven urethrovesical anastomosis was applied. In most cases, we performed posterior and anterior reconstructions [18] with minor modification using barbed suture. Furthermore, when indicated, we performed bilateral lymphadenectomy in either standard or extended template. Three surgeons with prior experience in performing 1018, 400, and 40 RPs of any type and 392, 366, and 20 RARPs were involved in the study.

2.3. IONM methods

We adopted total intravenous anesthesia by continuous intravenous infusion of propofol and remifentanil (bispectral index: 30–60) with controlled muscle relaxation. We controlled the train-of-four (TOF) count between 0 and 2, and neurologic tests were performed at a TOF count of 2 (ie, under less relaxed condition; Supplementary Fig. 1 and Supplementary material).

IONM was performed using NIM-Eclipse system (Medtronic Xomed, Inc., Jacksonville, FL, USA). Pudendal somatosensory evoked potential (SEP), bulbocavernosus reflex (BCR), and median nerve stimulation evoked CC-EMG (MNSE CC-EMG) were evaluated during baseline and final tests, which were performed just before trocar insertion and just

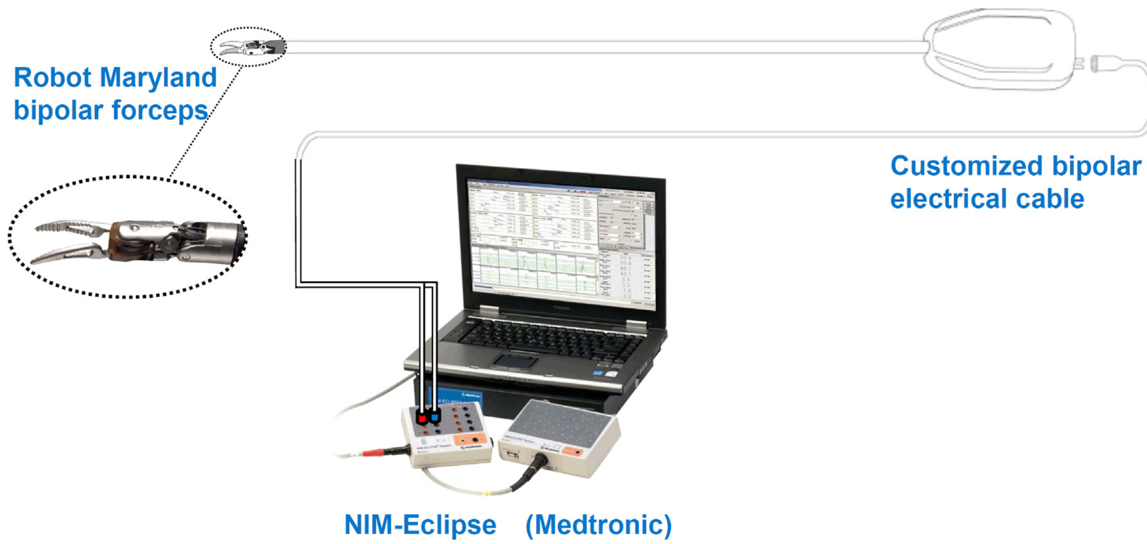

Fig. 1 – Stimulating Maryland bipolar forceps and circuit.

after drain insertion, respectively. Spontaneous and NVB-triggered CC-EMGs with various stimulation protocols were assessed just before NVB dissection and just after prostate removal. Stimulation was performed using da Vinci Maryland bipolar forceps (Intuitive Surgical, Sunnyvale, CA, USA) connected to a customized bipolar electrical cable and then to NIM-Eclipse (Fig. 1). CC-EMG was recorded by both surface electrodes and intracavernous subdermal needle electrodes, with reference electrodes in the ipsilateral suprapubic area (Fig. 2). Surface electrodes were placed at 4 and 8 o'clock positions in the proximal penile shaft, whereas subdermal needle electrodes were inserted into the corpus cavernosum at 2 and 10 o'clock positions in the middle penile shaft. All IONM tests were performed at resting state, with all manipulations stopped to exclude possible interference or artifact. All other information on IONM can be found in detail in the Supplementary material.

2.4. *Outcomes*

The primary outcome was the completion rate of planned IONM and surgery. The secondary outcomes were adverse events within 12 mo, quantification of NVB preservation, correlation between quantification and subjective nerve preservation grade [22] scored by the surgeon, and correlation between quantification of NVB preservation and postoperative potency recovery up to 12 mo.

2.5. *Measurements*

Potency and continence were evaluated at baseline and at 1, 3, 6, 9, and 12 mo after surgery. Potency recovery was defined as erection sufficient for sexual intercourse. Continence was evaluated by either zero pads or zero to one pad per day. Data from patient-reported questionnaires, five-level version of EuroQol-5 dimensions (EQ-5D-5L), Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP), and five-item version of International Index of Erectile Function (IIEF-5) were collected at baseline and at 3, 6, and 12 mo after surgery. Validated Korean versions of all questionnaires were used [23–25].

2.6. *Statistical analysis*

Data are expressed as mean $\pm$ standard deviation or percentage. Safety outcomes including completion rate and adverse events were evaluated in all patients. Efficacy outcomes were evaluated in patients after protocol setting. Statistical comparisons were tested using chi-square test for categorical variables, and *t* test or analysis of variance for continuous variables. Health-related utility value was converted using a validated conversion formula derived from the general Korean population [23]. All p values <0.05 were considered statistically significant.

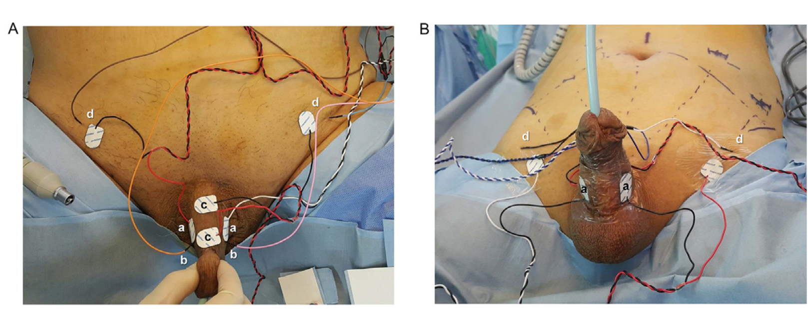

Fig. 2 – Electrode placement for corpus cavernosum electromyography: (A) dorsal view before fixation and (B) ventral view after fixation using medical adhesive film. The lowercase letters indicate the following: a—surface electrodes; b—subdermal needle electrodes; c—surface electrodes for pudendal somatosensory evoked potential stimulation; and d—reference electrodes.

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Table 1 – Characteristics of total patients and patients in efficacy analysis

	Total patients	Patients in efficacy analysis
No. of patients	30	22
Age (yr)	65.5 ± 5.3	66.2 ± 5.4
Body mass index (kg/m^2)	26.2 ± 3.1	25.9 ± 3.5
Comorbidity		
Hypertension	15 (50.0)	11 (50.0)
Diabetes mellitus	7 (23.3)	6 (27.3)
Vascular disease	6 (20.0)	4 (18.2)
Initial PSA (ng/ml)	12.2 ± 25.7	14.3 ± 29.9
Clinical T stage		
T1C	17 (56.7)	12 (54.5)
T2	11 (36.6)	8 (36.4)
T3A	2 (6.7)	2 (9.1)
Biopsy grade group		
1	11 (36.7)	6 (27.3)
2	5 (16.7)	4 (18.2)
3	6 (20.0)	5 (22.7)
4	6 (20.0)	5 (22.7)
5	2 (6.7)	2 (9.1)
Prostate size (ml)	40.0 ± 20.6	44.9 ± 22.5
Console time (min)	202.7 ± 56.7	214.2 ± 55.7
Estimated blood loss (ml)	368.3 ± 185.5	372.7 ± 186.9
Nerve sparing		
None	1 (3.3)	1 (4.5)
Unilateral	4 (13.3)	4 (18.2)
Bilateral	25 (83.3)	17 (77.3)
Lymph node dissection	12 (40.0)	10 (45.5)
Pathologic T stage		
T0 (vanishing cancer)	1 (3.3)	1 (4.5)
T2	16 (53.4)	9 (40.9)
T3A	9 (30.0)	8 (36.4)
T3B	4 (13.3)	4 (18.2)
Pathologic N stage		
N0	9 (30.0)	7 (31.8)
N1	3 (10.0)	3 (13.6)
Nx	18 (60.0)	12 (54.5)
Final pathologic grade group		
1	8 (26.7)	6 (27.3)
2	8 (26.7)	5 (22.7)
3	8 (26.7)	6 (27.3)
4	2 (6.7)	2 (9.1)
5	4 (13.3)	3 (13.6)
Tumor volume rate (%)	17.1 ± 21.0	20.4 ± 23.7
Positive surgical margin rate (%)	10 (33.3)	8 (36.4)
Preoperative potency	17 (57.2)	12 (54.5)
Baseline IIEF-5 score	12.7 ± 7.4	13.0 ± 7.3

IIEF-5 = five-item version of International Index of Erectile Function; PSA = prostate-specific antigen.
Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are expressed as number (%).

3. Results

Supplementary Fig. 2 shows the patient flow diagram. A total of 30 patients aged 56–73 yr with or without potency were enrolled. Following exclusion of eight initial cases prior to complete protocol setting, 22 patients were included in efficacy analysis. Characteristics of these patients are presented in Table 1.

With respect to the primary outcome, the completion rate of planned IONM and surgery was 100% (30/30). Only one patient (3.3%) experienced postoperative adverse events, which were Clavien-Dindo grade IIIb complications not related to IONM (deep vein thrombosis and prolonged leakage at the vesicourethral anastomotic site).

The time from the start of anesthesia to the start of console surgery was 92.8 ± 32.0 min (median, 90.0 min). The extra time for preparation was approximately 40–50 min. The sum of time for IONM test during surgery was approximately 40 min.

BCR was definitely observed at baseline and after surgery in all cases, except in one patient diagnosed with longitudinal extensive transverse myelitis. Definitive pudendal SEP was observed in only 18.2% of patients (4/22; Table 2); furthermore, pudendal SEP did not change postoperatively.

Waveforms of NVB-triggered CC-EMG, sporadic spontaneous CC-EMG, or MNSE CC-EMG were not distinguishable. CC-EMGs were typically low-frequency, polyphasic signals lasting for 8–12 s (Fig. 3A) [15,16,26]. NVB-triggered CC-EMG was observed during and/or after stimulation (Fig. 3B). NVB-triggered CC-EMG during stimulation was usually repeated continuously throughout the entire stimulation period. Subsequent NVB-triggered CC-EMG after stimulation was typically observed within 10 s after finishing stimulation and for at least 30 s. Although we stimulated one side of the NVB, CC-EMG was synchronously recorded from the bilateral corpus cavernosum in most cases. When simultaneously recorded, CC-EMG recordings from surface electrodes and subdermal needle electrodes were always concurrent. Thus, we interpreted them complementarily. We could quantify CC-EMG signal as 0 (not observed), 1 (weak positive), and 2 (strong positive). Accordingly, we quantified spontaneous and MNSE CC-EMGs as grades 0–2 and NVB-triggered CC-EMG as grades 0–4, which were the sum of bilateral NVB stimulation results.

Table 2 – Corpus cavernosum electromyographies before prostate removal and preoperative IIEF-5 scores

Grade	Pudendal somatosensory evoked potential	Spontaneous CC-EMG	Median nerve stimulation evoked CC-EMG	NVB-triggered CC-EMG
0	11.3 ± 7.9 (10)	3.7 ± 1.5 (3)	5.0 ± 2.9 (4)	3.7 ± 1.5 (3)
1	13.6 ± 5.3 (8)	11.8 ± 7.1 (8)	11.0 ± 6.8 (6)	6.0 ± 4.2 (2)
2	15.8 ± 9.7 (4)	16.4 ± 5.9 (11)	16.6 ± 6.2 (12)	13.2 ± 6.8 (6)
3				15.0 ± 3.6 (3)
4				17.3 ± 7.0 (8)
p value	0.578	0.015	0.009	0.025

CC-EMG = corpus cavernosum electromyography; IIEF-5 = five-item version of International Index of Erectile Function; NVB = neurovascular bundle
Patient number assigned is given within parentheses.

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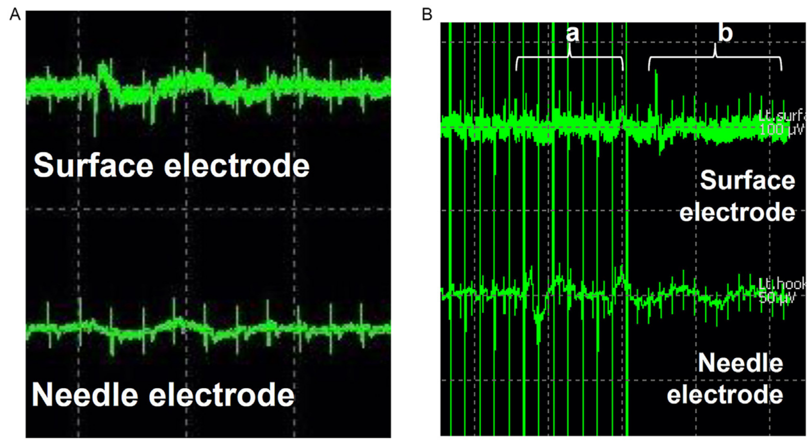

Fig. 3 – Example of corpus cavernosum electromyography (CC-EMG): (A) strong positive spontaneous CC-EMG and (B) neurovascular bundle-triggered CC-EMG. CC-EMG during stimulation (a) is visible, and subsequent CC-EMG after stimulation (b) is observed at approximately 2 s later for a duration of 9 s (5 s/division).

Quantification of NVB preservation in preoperatively impotent men was difficult because CC-EMG grades after prostate removal reflected both postoperative status and preoperative erectile function. Thus, we could not correlate quantification with subjective nerve preservation grade. However, all three CC-EMGs before prostate removal were significantly associated with preoperative erectile function evaluated by IIEF-5 (Table 2). Pudendal SEP showed a similar trend, albeit without significance. Furthermore, all three CC-EMGs after prostate removal were significantly associated with potency recovery and IIEF-5 score (Fig. 4 and Supplementary Fig. 3). CC-EMGs after prostate removal were associated with continence recovery at certain time points (Supplementary Fig. 4). Patients with a higher grade recovered faster, and only patients with grade 0 did not achieve continence recovery at 1 yr.

Changes in EQ-5D-5L and EPIC-CP scores in all patients are presented in Table 3. With respect to EQ-5D-5L, utility values did not change significantly, but the visual analog scale score decreased significantly. With respect to EPIC-CP, deteriorated urinary function recovered at 12 mo, but sexual function did not.

4. Discussion

Since the introduction of CaverMap (UroMed Corp., Boston, MA, USA), several groups have suggested electroneurophysiologic IONM methods for cavernous nerve detection [8–12]. They used electrical stimulation but measured indirect response, tumescence, or cavernosal pressure. Moreover, the response to cavernosal pressure, which was increased, decreased, or mixed, was complex to interpret. The change in cavernosal pressure could have also occurred as a result of anesthetic use, surgical manipulation, and several other factors. Consequently, the specificity of CaverMap was only 54%. Virtually, all patients showed a positive response after prostate removal. Furthermore, the response took several minutes, and the techniques were thus impractical.

Therefore, we revisited an old technique—CC-EMG, which represents direct electrical neuronal response with impedance change inside the corpus cavernosum [14–17,26]. The response time for impedance change is usually within several seconds, and an observation time of <30 s is sufficient. We revived spontaneous, MNSE, or cavernous nerve-triggered CC-EMG as IONM during RP for the first time.

The source of spontaneous CC-EMG was traditionally thought to be a sympathetic suppression signal [14–16,26]. MNSE CC-EMG is known to be mediated by the sympathetic nervous system [17]. The cavernous nerve contains both sympathetic and parasympathetic nerve fibers, but is believed to be parasympathetic dominant. Actually, cavernous nerve stimulation, and not median nerve stimulation, is commonly observed to induce tumescence in potent men. Notwithstanding this difference in source, our findings suggest an almost identical shape and pattern among the three CC-EMGs, which are in agreement with previous descriptions [15–17]. Furthermore, we observed that they all reflected integral erectile function. As for NVB-triggered CC-EMG, recording a positive signal in preoperatively impotent men was difficult, even with an intact cavernous nerve. Thus, we think that sexually potent patients will benefit from this technique. A possible explanation is that CC-EMG is not an action potential conducted through the cavernous nerve. Electrical potentials may passively spread via intercellular diffusion through intercellular gap junctions inside the corpus cavernosum. CC-EMG's polyphasic slow wave complex may reflect this kind of synchronous electrical activities. Therefore, CC-EMG requires an intact neural pathway, healthy corpus cavernosal endothelial cells, adequate blood supply, and intact erectile function.

Among the three CC-EMGs, NVB-triggered CC-EMG seems to be the most useful. Spontaneous CC-EMG requires a longer observation time (usually 1 min). Spontaneous and MNSE CC-EMGs reflect only erectile function. In comparison,

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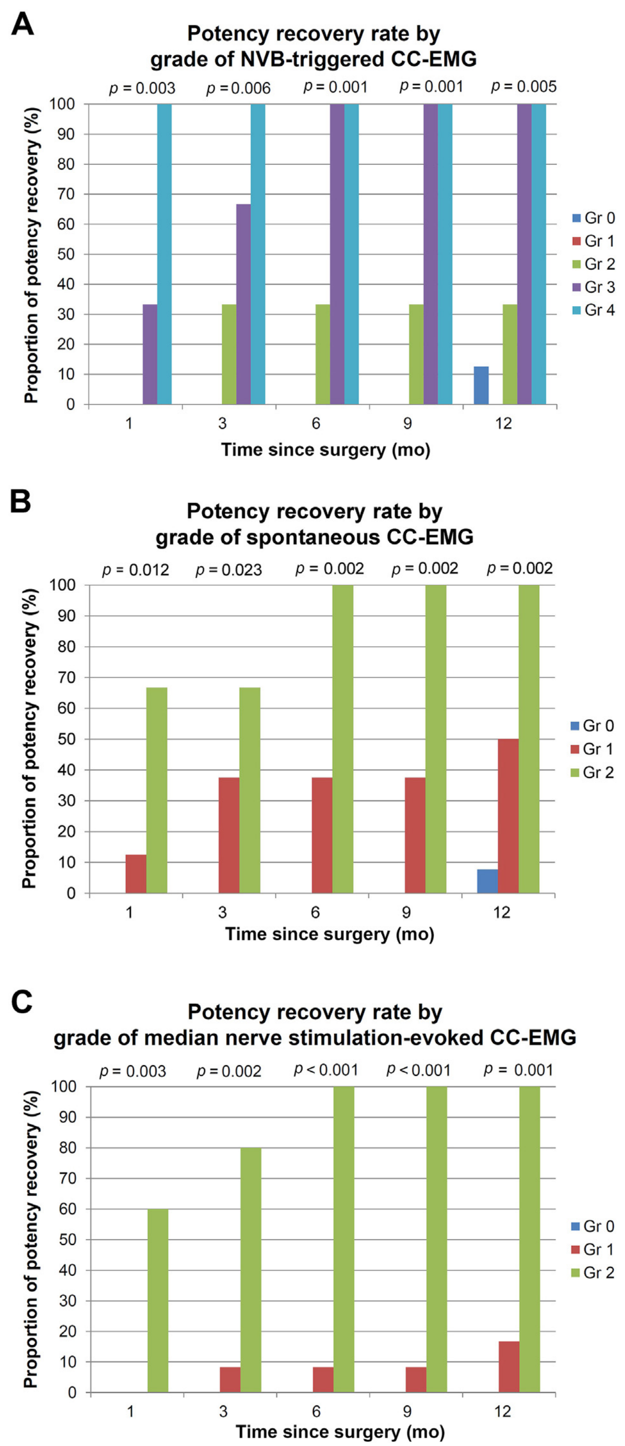

Fig. 4 – Grade of corpus cavernosum electromyographies after prostate removal and potency recovery: (A) neurovascular bundle-triggered CC-EMG, (B) spontaneous CC-EMG and (C) median nerve stimulation-evoked CC-EMG. CC-EMG = corpus cavernosum electromyography; Gr = grade; NVB = neurovascular bundle.

cavernous nerve-triggered CC-EMG further adds site-specific neural pathway information. Furthermore, we could make a five-tiered grade that combines right and left three-tiered responses. At this time, we can predict potency recovery or compare surgical techniques with respect to erectile function preservation using this CC-EMG grade. By increasing its sensitivity and spatial resolution, we could use it as a good nerve-mapping technique and perform more precise nerve-sparing surgery.

Table 3 – Change in patient-reported quality of life within 1 yr (*N* = 30)

	Baseline	3 mo	6 mo	12 mo
EQ-5D-5L				
Utility	0.92 ± 0.10	0.87 ± 0.14	0.88 ± 0.16	0.89 ± 0.15
Visual analog scale	82.7 ± 13.8	76.4 ± 11.2	75.8 ± 13.7[a]	73.8 ± 18.1[a]
EPIC-CP				
Urinary incontinence	2.2 ± 2.0	4.6 ± 3.8[a]	3.4 ± 2.4[a]	2.9 ± 2.6
Urinary irritation/ obstruction	3.6 ± 3.5	2.8 ± 3.0	2.1 ± 2.0[a]	2.4 ± 2.7
Bowel	3.4 ± 4.3	2.1 ± 2.9	1.4 ± 2.1[a]	2.1 ± 3.5
Sexual	5.2 ± 3.1	8.4 ± 4.1[a]	8.4 ± 3.4[a]	8.3 ± 3.0[a]
Vitality/hormonal	2.2 ± 4.0	1.3 ± 2.4	1.5 ± 2.8	2.4 ± 4.0
Total	16.7 ± 13.7	19.2 ± 11.1	16.7 ± 9.5	18.0 ± 2.1

EPIC-CP = Expanded Prostate Cancer Index Composite for Clinical Practice; EQ-5D-5L = five-level version of EuroQol-5 dimensions.
[a] Paired *t* test, $p < 0.05$.

This study is not without limitations. We initially performed cavernous nerve localization test; however, we discarded this evaluation during the protocol-setting period owing to time constraints. Thus, this technique's mapping ability and spatial resolution should be further evaluated. We could not filter signal at <1 Hz owing to device limitation. Hence, we might have lost information and have lower CC-EMG amplitude. However, we think that the presence of CC-EMG itself is important and it is not difficult to detect. We should further evaluate whether low-pass filtering (0.1–50 Hz) can improve sensitivity or spatial resolution. We used relatively high stimulation intensity (30 mA) because capturing response is primarily important, considering that this study is the first-in-human study. A lower intensity between 5 and 30 mA with a shorter duration might be sufficient and should be tested to achieve better performance. Additionally, preparation and test for the IONM technique took approximately 60–90 min. However, considering that the present study is the first feasibility study to test various protocols, this could be reduced in the future when a simplified protocol is applied with experience. A relatively high rate of comorbidity such as hypertension or diabetes could affect pre- and postoperative erectile function. Although controversial [27], pelvic lymphadenectomy was performed in almost 50% of patients, which could influence postoperative potency recovery.

As a future direction, NVB-triggered CC-EMG using surface electrodes at the bilateral penile body may be sufficient for clinical purpose. Stimulator design, stimulation methods, and device setting should be explored further to improve test performance. In the clinical setting, surgeons may check cavernous nerve–triggered CC-EMG wherever they want prior to cutting, electrocautery, or suturing to avoid nerve injury. Careful inspection not only around the pedicle but also in the apex area is very important to preserve the cavernous nerve. Phase II trials evaluating this technique with aforementioned revised methods that can actually improve erectile function preservation in larger patient cohorts are warranted.

5. Conclusions

We successfully established the protocol for IONM using CC-EMG during RARP. Our results suggest that this technique is feasible and safe. Spontaneous, MNSE, and NVB-triggered CC-EMGs before prostate removal well reflected preoperative erectile function. Furthermore, CC-EMGs after prostate removal well predicted potency recovery. This IONM technique remains investigational; nonetheless, further optimization of this technique to improve its clinical usefulness, particularly for cavernous nerve–triggered CC-EMG, seems worthy. After refining the technique, larger prospective clinical trials with simplified protocol are warranted to evaluate whether it can actually improve postoperative erectile function.

Author contributions: Chang Wook Jeong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jeong, K. Kim, Seo.
Acquisition of data: Jeong, Park, Tae, S.-M. Kim, Hur, K. Kim, Ku, Kwak, H.H. Kim.
Analysis and interpretation of data: Jeong, K. Kim, Song.
Drafting of the manuscript: Jeong, Song, K. Kim.
Critical revision of the manuscript for important intellectual content: Park, Tae, S.-M. Kim, Hur, Seo, Ku, Kwak, H.H. Kim.
Statistical analysis: Jeong, Song.
Obtaining funding: Jeong.
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Other: None.

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Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at https://doi.org/10.1016/j.eururo.2019.04.042 and via www.europeanurology.com.

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