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Enhancing Hemodialysis Efficacy through Neuromuscular Stimulation

Guruprasad Madhavan[a, b] Mary A. Nemcek[a, c] David G. Martinez[d, e] Kenneth J. McLeod[a, b]

[a]Clinical Science and Engineering Research Center, [b]Department of Bioengineering, [c]Decker School of Nursing, State University of New York and [d]United Health Services Renal Care Center, Binghamton, N.Y., and [e]State University of New York – Upstate Medical University, Syracuse, N.Y., USA

Key Words
Blood pressure · Calf muscle pump · Cardiovascular refilling · Intradialytic hypotension · Ultrafiltration · Neuromuscular stimulation

Abstract
Beat-to-beat blood pressure monitoring was used to assess the efficacy of reflex-mediated, calf muscle pump stimulation to enhance cardiovascular refilling in subjects in the supine and seated positions, with extension of this stimulation technology to dialysis evaluated in 2 dialysis patients. Micromechanical stimulation (50 μm at 45 Hz) of the plantar surface was found to significantly increase both the rate and volume of cardiovascular refilling relative to that observed for subjects in the supine position. During hemodialysis, calf muscle pump stimulation permitted significantly increased ultrafiltrate removal, specifically from 78 to 96% of clinical goal, while serving to maintain both blood pressure and blood volume.

Introduction

Recent prospective studies have shown that attainment of hemodialytic clinical performance targets significantly improves patient outcomes, including hospital admissions, health care costs, and mortality [1]. One of the continuing challenges in attaining clinical outcomes is acute hypovolemia resulting from ultrafiltration and inadequate compensatory mechanisms, specifically the rate of cardiovascular refilling. Inadequate compensation arises under conditions of abnormal venous compliance, excessive microvascular filtration, impaired venous return, or inadequate interstitial fluid recovery from the lower extremities [2–4]. Vasopressive pharmacologic agents [5], ultrafiltrate profiling [6], and dialysate cooling techniques [7] have all been investigated as means for improving patient tolerance for dialysis; however, these regimens have been only marginally effective or poorly tolerated given their extensive side effects [8–10]. Nonpharmacologic methods such as high-intensity exercise training [11] or low-frequency electrical stimulation for improving fluid mobilization, mainly through enhancement of calf muscle pump activity, have also been pursued, but these approaches are typically underemployed due to patient reticence or discomfort [12].

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Kenneth J. McLeod, PhD
Department of Bioengineering, Clinical Science and Engineering Research Center
State University of New York
Binghamton, NY 13902-6000 (USA)
Tel. +1 607 777 5779, Fax +1 607 777 5780, E-Mail kmcleod@binghamton.edu

An alternative approach for mobilizing interstitial fluid and accelerating cardiovascular refilling is to use postural reflex pathways to indirectly activate the calf muscle pump. Postural muscles, such as the soleus, are receptive to a wide range of cutaneous somatosensory inputs via spinal and supraspinal reflex arcs originating on the plantar surface [13, 14]. Micromechanical stimulation (50 μm at 45 Hz) of the plantar surface has been shown to be capable of limiting orthostatic hypotension via plantar-based Meissner's corpuscles [14, 15]. This stimulus has also been shown to double the lymphatic return pressure in the subjects during upright tilt [16] and significantly reduce lower limb edema during quiet sitting [17].

Based on these results, we hypothesized that plantar micromechanical stimulation may be capable of significantly enhancing cardiovascular refilling in dialysis patients and therefore could assist in the reduction of complications of dialysis such as hypotensive episodes. To address this hypothesis, we undertook studies to characterize: (1) cardiovascular refilling when in the supine position; (2) cardiovascular refilling while seated and experiencing plantar stimulation, and (3) the ability of plantar stimulation to enhance cardiovascular refilling and increase the attainment of clinical goals in dialysis patients.

Methods

Study protocols were approved by the Institutional Review Boards at Binghamton University and the United Health Services Hospitals, Binghamton, N.Y., USA. Voluntary written informed consent was obtained from each study participant prior to the session.

Men and nonpregnant women between the ages of 35 and 80 were recruited. Inclusion criteria for the dialysis subjects were intact plantar sensation and demonstration of consistent intradialytic hypotensive events, defined as a drop in systolic blood pressure (SBP) $\geq$40 mm Hg or other symptoms requiring repeated termination of dialysis sessions. Exclusion criteria for the dialysis subjects included any neuromuscular condition affecting plantar sensation, uncontrolled hypertension (with medications), presence or past history of deep venous thrombosis, or history of pulmonary embolism.

A beat-to-beat finger blood pressure monitoring system was used to obtain continuous blood pressure monitoring (Portapres Model 2, TNO-BMI; Finapres Medical Systems, Amsterdam, The Netherlands). Calf muscle pump stimulation was implemented by means of a plantar micromechanical stimulation device (Juvent Medical, Inc., Somerset, N.J., USA). The device has been evaluated by the US Food and Drug Administration to be of nonsignificant risk as defined by the Investigational Device Exemption Regulation. The device delivers a sinusoidal 45-Hz, 50-μm (peak-to-peak) displacement to the plantar surface of the subjects. For the laboratory studies, the device (approximately 40 × 40 × 8 cm) was placed flat on the floor in front of the seated subjects. For the dialysis study, a custom apparatus was developed to hold the stimulation device at an appropriate height and angle so that the stimulator could be supported against the plantar surface of the patients' feet during dialysis, permitting continued calf muscle pump stimulation while the subjects were reclining in the dialysis chair.

Standard hemodialysis procedures were carried out with the end-stage renal disease (ESRD) patients at the United Health Services Renal Care Center (Binghamton General Hospital) on System 1000 Althin hemodialysis units (First International Medical, Chicago, Ill., USA) using EXELTRA High-Flux, Single-Use Dialyzers (Baxter, Deerfield, Ill., USA). A semi-automatic arm cuff (Datascope Passport 2; SOMA Technology, Inc., Cheshire, Conn., USA) interfaced with the hemodialyzing system was used for blood pressure measurements every 30 min. Hematocrit-based relative blood volume measurements were carried out once every 30 min through an optical density monitor (CRIT LINE III, Hemametrics, Kaysville, Utah, USA).

Laboratory Evaluation of Cardiovascular Refilling in Supine and Seated Adults

After obtaining informed consent, the subjects were advised to remove bracelets and wristwatches to avoid possible interference with the measurements. A remote-controllable power recliner was utilized to lower the subjects into the supine position and raise them to the seated position without muscular effort.

Subjects being evaluated for cardiovascular refilling during supine rest were reclined for an overall duration of 95 min during which time SBP, diastolic blood pressure (DBP), and heart rate (HR) were continually recorded. Subjects undergoing plantar stimulation first underwent a 30-min rest in the supine position, and were then elevated to a seated position where they completed two sequential 30-min exposures. The first involved quiet sitting for 30 min with the subjects' feet on an inactivated plantar stimulation device placed on the floor. This was followed by an additional 30 min of sitting with the application of plantar stimulation.

Cardiovascular Refilling during Dialysis

Subjects in the dialysis study were undergoing standard hemodialysis treatment three times a week (Monday, Wednesday, and Friday). The patients received plantar micromechanical stimulation during their regular 4-hour (6:00–10:00 a.m.) treatment sessions on Wednesdays and Fridays during an 8-week period. For consistency, Monday treatment sessions were not examined because of the 3-day gap between treatments. The primary outcome for the dialysis study was percent ultrafiltrate removed relative to the daily treatment goal. Comparison data for the dialysis patients were obtained from the dialysis unit record books for the 8 weeks immediately prior to the experimental period.

Assessment and Statistical Analysis

For the supine study, all blood pressure and HR data were normalized to a value of zero at the time when the subjects were first reclined. For the seated study, all blood pressure and HR data were normalized to a value of zero at the time when the subjects were raised to the seated position. These normalizations permitted the datasets to be averaged. The initial and final 60 measurements of

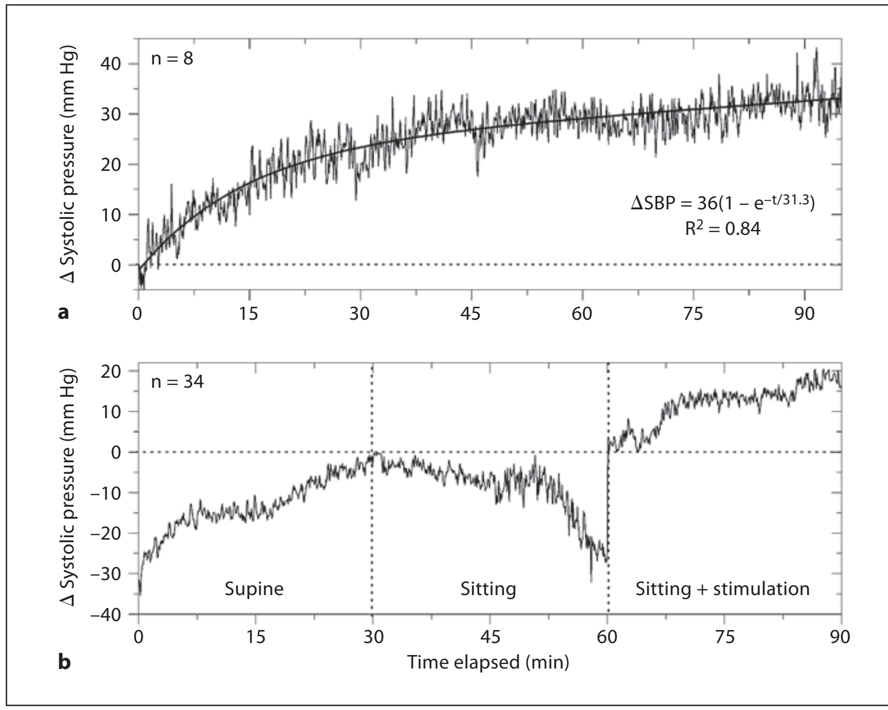

Fig. 1. a Average temporal response of the SBP of 8 healthy adult women over a duration of 95 min of supine rest. A significant increase in SBP of 35 mm Hg ($p < 0.001$) was observed. Curve fit to a decaying exponential function identified a time constant of 31.3 min ($R^2 = 0.84$), consistent with a refilling time of about 2.5 h. **b** Response of SBP in 34 healthy adult women to supine rest (0–30 min), quiet upright sitting (30–60 min), and plantar micromechanical stimulation (60–90 min). The normalized values of the SBP increase during supine rest are lower than those observed in **a** consistent with the fact that complete refilling has not yet occurred. SBP exhibited decreases during the 30-min quiet sitting regimen approximately equal to the increase observed during supine rest, and consistent with the gravity-induced extravasation of plasma into the interstitial spaces of the dependent tissues and venous and lymphatic pooling. With the initiation of plantar stimulation, SBP increased abruptly followed by a slower sustained increase over the subsequent 30 min, resulting in a total increase in SBP of almost 45 mm Hg.

blood pressure and HR values were used for t test comparisons. For the dialysis sessions, values of SBP, ultrafiltrate removed, and blood volumes were averaged for both the pretreatment and treatment periods over 8 weeks. All data are expressed as means ± SEM.

Results

All subjects screened for the laboratory studies were women. Eight subjects were randomly assigned to the supine group and 34 to the seated group. The subjects in the supine and seated laboratory studies had an average age of 52.1 ± 3.1 years and 53.8 ± 1.9 years, and a BMI of 27.4 ± 1.3 and 26.7 ± 0.7, respectively. The starting SBP and DBP values for the supine study group were 123.2 ± 3.1 mm Hg and 67.1 ± 2.3 mm Hg, and for the seated study group they were 124.9 ± 2.1 mm Hg and 64.9 ± 1.7 mm Hg, respectively. Only HR values at the start of the supine rest were observed to be significantly different between the two laboratory study groups (71.4 ± 2.9 bpm) and the test group (64.9 ± 1.7 bpm).

Supine Study

In 8 subjects, 95 min of supine rest resulted in a significant rise in both SBP (33 mm Hg; $p < 0.0001$) and DBP (17 mm Hg; $p < 0.0001$), as well as a significant decrease in HR (7 bpm; $p < 0.0001$). Regression analysis showed that the blood pressure time course changes could be accurately characterized by a declining exponential function. Averaged SBP time course data demonstrated a total increase of 36 mm Hg with a time constant of 31.3 min ($R^2 = 0.84$), indicating an SBP recovery time in healthy adults of approximately 2.5 h, using the traditional definition of five time constants (fig. 1a). Averaged DBP time course data showed a total increase of 20 mm Hg with a time constant of 52 min ($R^2 = 0.82$), indicating a complete

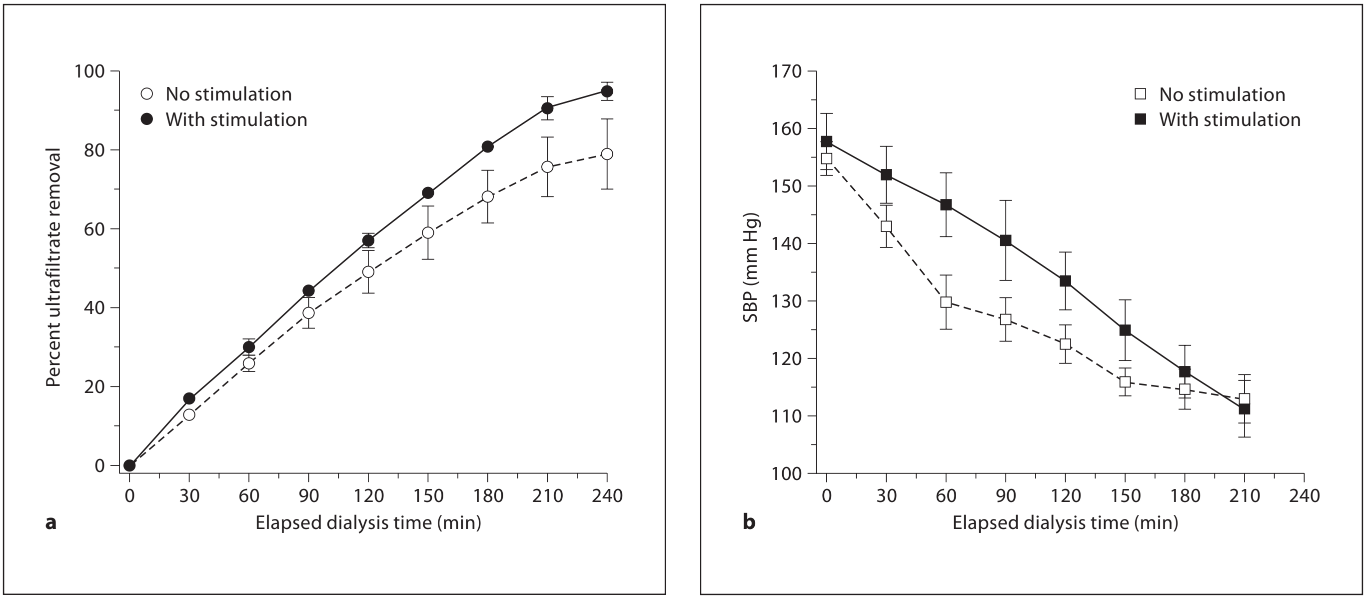

Fig. 2. Efficacy of plantar-based calf muscle pump stimulation to enhance attainment of clinical goals. **a** Average ultrafiltrate goal attained in the 8 weeks prior to the start of the plantar stimulation treatment (○) was 78 ± 8.9% while with stimulation (●) it was increased to 96 ± 2.3%. **b** Without plantar stimulation (□), the average SBP of the 2 ESRD subjects fell >25 mm Hg within the first hour of dialysis and >40 mm Hg within 2.5 h. With stimulation (■), development of hypotension was delayed substantially with average SBP falling approx. 10 mm Hg in the first hour and by 45 mm Hg after 3.5 h.

cardiovascular refill time slightly exceeding 4 h when transitioned from an upright to supine position. The fit to the averaged HR data yielded a time constant of 23 min ($R^2 = 0.63$).

Seated Study

Thirty-four healthy female subjects underwent 30 min of supine rest followed by 30 min of quiet upright sitting. Thirty minutes of supine rest resulted in an average increase in SBP of 26 ± 1.1 mm Hg, an average elevation in DBP of 12 ± 0.4 mm Hg, and an average decrease in HR of 6 ± 0.7 bpm. The transition to upright sitting resulted in a corresponding mean decrease in SBP of 26 ± 0.7 mm Hg, an average drop in DBP of 15 ± 0.3 mm Hg, and an average increase in HR of 7 ± 0.3 bpm. Application of plantar stimulation while the subjects remained seated resulted in a rapid increase in SBP of approximately 30 mm Hg, bringing the average SBP back to the approximately same level as observed at the start of the seated protocol (fig. 1b). Continued application of plantar stimulation over the subsequent 30 min resulted in further increases in average SBP of 16 ± 0.5 mm Hg, resulting in a total increase in SBP of 46 mm Hg. Similarly, DBP was observed to rapidly increase by 15 mm Hg at the onset of plantar stimulation, and then rose an additional 9 ± 0.5 mm Hg with continued stimulation. HR dropped 7 bpm shortly after the initiation of the stimulus, with a further drop in average HR of 6 ± 0.5 bpm with continued stimulation.

Dialysis Study

Two male ESRD patients (aged 52 and 58 years) were recruited for the clinical phase of the investigation. The average estimated dry weight and ultrafiltrate removal goal for the patients were 115 ± 2.5 and 4.4 ± 1.3 kg, respectively. The effect of treatment on the attainment of clinical goals was evaluated by determining the fraction of the ultrafiltrate goal achieved during each dialysis session (fig. 2a). The average percent of the dialysis goal attained in the 8 weeks prior to the start of the calf muscle pump stimulation treatment was 78 ± 8.9% and during the study period with stimulation it was 96 ± 2.3%. Enhanced ultrafiltrate removal was obtained primarily in the third and fourth hours of dialysis. Final blood volume assessed using hematocrit values following 3.5 h of dialysis was found to have decreased 10.8 ± 2.3% with plantar stimulation as compared to 11.4 ± 1.0% in the absence of stimulation. In the absence of plantar stimulation the average SBP of the 2 subjects fell by more than 25 mm Hg within the first hour of dialysis and by more than 40 mm Hg within 2.5 h (fig. 2b). With continued stimulation, the average SBP for the 2 subjects fell just over 10 mm Hg in the first hour, and by 45 mm Hg after 3.5 h.

Discussion

In this study, blood pressure was used as a surrogate measure of the status of cardiovascular refilling. In the initial study on supine subjects, we observed that extended supine rest resulted in substantial cardiovascular refilling, increasing SBP by 36 mm Hg, and DBP by 20 mm Hg, but this refilling required upwards of 4 h. Previous work on recovery of interstitial fluid, such as that reported by Tarazi et al. [18], Hagan et al. [19], and Jacob et al. [20], has shown that cardiovascular refilling occurs within tens of minutes following a brief period of upright posture. Our seated studies confirm that fluid pooling into dependent tissue is readily reversible following transient changes in posture, therefore, the 4-hour recovery time course is consistent with the fact that our subjects had been upright 4 or more hours before undergoing testing in our laboratory, and so had likely pooled considerable fluid into the tissues of the lower body.

Micromechanical stimulation of the calf muscle pump was found to result in substantially larger and faster changes in blood pressure than occurred during supine rest. During plantar stimulation we observed two distinct phases of blood pressure change. In the first phase, we observed an immediate 30 mm Hg rise in SBP. Given that this rise occurred within seconds we believe this is indicative of the rapid return to the heart of blood and lymph pooled in the major veins and lymphatics of the lower limbs. In the second phase of the response, we observed slow increases in SBP and DBP similar to those observed during the extended supine testing. When the initial rapid rise in SBP is combined with the longer, slow rise, the result was a total average increase in SBP of approx. 45 mm Hg in 30 min, which is substantially greater than the 36 mm Hg increase in SBP which required more than 2 h of supine rest. Similarly, DBP was increased more than 28 mm Hg with 30 min of stimulation. The implication is that plantar stimulation increased the rate of cardiovascular refilling by a factor of at least 6- to 10-fold.

That enhanced cardiovascular refilling produced by calf muscle pump stimulation could be useful in assisting in the attainment of clinical goals in ESRD patients appears to be supported by our initial clinical data. The stimulation permitted a sustained ultrafiltration rate which led to the removal of 96% of the desired fluid volume, compared to only 78%, on average, in the absence of calf muscle pump stimulation. Further, the drop in SBP in the 2 subjects who had a history of chronic intradialytic hypotensive events was significantly slowed, though even with plantar stimulation the average drop in SBP in these 2 subjects reached 45 mm Hg over the 4-hour dialysis treatment period. The fact that the stimulation is both passive and painless likely contributed to the high levels of compliance observed.

In summary, plantar-based, reflex-mediated calf muscle pump stimulation significantly accelerates cardiovascular refilling, mobilizing more lower limb fluid in 30 min than occurs during 4 h of supine rest in healthy subjects. The implications of these results are evident from the ability of this treatment to improve clinical outcome in dialysis patients who commonly suffer from intradialytic hypotensive events during dialysis. Specifically, the results of a small pilot clinical trial show an increase in the amount of ultrafiltrate removed during dialysis, from 78 to 96% of the clinical goal, while significantly delaying SBP drops and limiting the decrease in blood volume.

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Disclosure

Kenneth J. McLeod has a financial interest in Juvent Medical, Inc., Somerset, N.J., USA. The research reported in this article may confer a benefit upon Juvent Medical, Inc.

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