ELSEVIER

Sleep Medicine 6 (2005) 101–106

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Enhanced external counter pulsation (EECP) as a novel treatment for restless legs syndrome (RLS): a preliminary test of the vascular neurologic hypothesis for RLS

Sri-Sujanthy Rajaram[a], Jewel Shanahan[b], Carol Ash[a], Arthur S. Walters[c,*], Gerald Weisfogel[a]

[a]*Cardio-Sleep Center, Old Bridge, Edison, NJ, USA*
[b]*ECP Heart Center, Old Bridge, NJ, USA*
[c]*New Jersey Neuroscience Institute at JFK Medical Center, Seton Hall University School of Graduate Medical Education, 65, James Street, Edison, NJ 08818, USA*

Received 12 July 2004; received in revised form 11 October 2004; accepted 22 October 2004

Abstract

Background and purpose: Enhanced external counter pulsation (EECP) is used to treat angina. With sustained treatment this increases collateral circulation to the coronary arteries as well as to the body as a whole. We found some patients who underwent EECP for angina or congestive heart failure who also coincidentally had severe Restless Legs Syndrome (RLS). Case reports are presented.

Patients and methods: Six patients with RLS (1F, 5M, ages 55–80) underwent EECP treatment. All patients were given the International RLS Study Group rating scale for RLS (the IRLS) before and immediately after 35 days of EECP treatment.

Results: The average IRLS rating scale score of the six patients before treatment was 28.8 (range 23–35), which indicates frequent and moderate to very severe RLS. After 35 days of EECP treatment the IRLS score was 6 ($P < 0.03$), which indicates clinically insignificant RLS. Long-term follow-up in three patients indicates sustained improvement in all three at 3–6 months after EECP was completed (IRLS score 28.3–3.33). Further follow-up in four patients showed sustained improvement in two patients 1 year after EECP was completed.

Conclusion: EECP improves RLS symptoms significantly and could be considered as an adjunct treatment for patients with RLS. In some cases, the improvement lasts for months after the course of treatment. In this way EECP is unique and unlike pharmacotherapy which requires continuous daily treatment. Furthermore, our results suggest that decreases in vascular flow influence the peripheral or central nervous system leading to the sensory symptoms of RLS. A larger number of patients studied under blinded conditions is needed to draw further conclusions.

Keywords: Restless legs syndrome; Enhanced external counter pulsation

1. Introduction

The vascular hypothesis for restless legs syndrome (RLS) was in vogue in the 1940s and 1950s, but has been little explored since then. Coccagna et al. [1] recently reviewed the history of this hypothesis. Briefly stated, the hypothesis is that decreased blood flow leads to symptoms of RLS. In 1943, Allison [2], a sufferer of restless legs syndrome himself, was one of the first to propose this hypothesis. Ekbom favored a vascular cause and recommended vasodilators as prime therapy [3,4]. Vasodilators have fallen out of favor for the treatment of RLS in recent times, and there have been no double-blind trials of vasodilators for RLS. Bonduelle and Jolivet [5–8] suggested that the origin of RLS was a circulatory disturbance in the lumbar spine, consisting of slowing of venous flow triggered by decubiti or pregnancy. In more modern times LaBan [9] briefly revived this hypothesis implicating lumbar spinal stenosis as pathogenic. Kanter et al. [10] also recently reported that some people with RLS who have coexisting

* Corresponding author. Tel.: +1 732 321 7000x68177; fax: +1 732 632 1584.
E-mail address: artumdnj@aol.com (A.S. Walters).

1389-9457/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.sleep.2004.10.012

varicose or spider leg veins may find that their RLS symptoms improve after treatment of their vein condition by 'sclerotherapy'. Although symptoms may recur gradually over time, re-treatment of recurrent veins is thought to bring further improvement in RLS symptoms.

Enhanced external counter pulsation (EECP) is used in patients with angina refractory to medical therapy and who are not readily amenable to surgical intervention [11]. It is also used to treat patients with congestive heart failure [12] and vascular impotence [13]. With sustained treatment for an hour a day over 35 days, it works by increasing collateral circulation to the heart and probably to the microvasculature in the body as a whole, including the legs. EECP may also work via neurohumeral effects [14,15].

We found that some patients with concomitant severe RLS coincidentally showed significant improvement in RLS symptoms following EECP. We also found RLS patients with diabetic peripheral neuropathy whose symptoms of peripheral neuropathy subjectively improved after EECP. We are therefore presenting the case reports of four of our six patients who underwent EECP.

To our knowledge this is the first study of EECP for the symptoms of RLS. The following case reports are for four of our six RLS patients who underwent EECP. Refer to the Table 1 for patient number.

2. Case reports

2.1. Patient 1

This is a 64-year-old man who has had symptoms of RLS for 23 years. He meets criteria for RLS by International Restless Legs Syndrome Study Group (IRLSSG) [16]. His symptoms are characterized by the need to move although he has no definite leg sensations. His symptoms are worse at night, worse sitting or lying down and he experiences significant relief by moving around. Prior to EECP his symptoms occurred 4–5 times per week and lasted about 2–3 h per night, which resulted in significant sleep disruption. He is not aware of any twitching or involuntary jerking of the legs either while awake or sleeping. He has never been diagnosed with RLS. There is no family history of RLS.

He has a history of diabetes mellitus, hypertension, hypercholesterolemia and severe coronary artery disease. He had a myocardial infarction in 1986 and three stents were placed in his coronary arteries in 1999. He had shortness of breath prior to stent placement and had no significant improvement after the stent placement. He also had peripheral vascular disease and underwent carotid artery stenting and left femoral bypass in 2003. He is scheduled for right femoral bypass surgery this year. He was not on any medications to improve the symptoms of RLS.

This patient first underwent EECP treatment for 35 days 3 years ago, which resulted in significant improvement in his shortness of breath. He also noticed all of his symptoms of RLS disappeared with the treatment.

One year ago he underwent repeat EECP treatment for 35 days. At baseline prior to the second course of EECP his International Restless Legs Syndrome Study Group Rating Scale (IRLS) score was 26, which indicates moderate to severe RLS [17,18]. Directly after completion of EECP treatment his IRLS score went down to 0 and remained at 0 after 1 year. The patient also reported absence of any RLS symptoms during the year after EECP, which indicates a sustained improvement that is also long lasting. He also noted improvement in his ability to feel pain and light touch, which is suggestive of some improvement in his diabetic peripheral neuropathy.

On neurological examination 1 year after EECP, there was no weakness, and pinprick and position sense were normal. Vibration was decreased in the toes and ankles more prominently in the right lower extremity. Muscle stretch reflexes were absent in the ankles and knees, but normal in the upper extremities. This is most consistent with mild diabetic peripheral neuropathy primarily involving the lower extremities.

Table 1
Demographics and treatment response of six Restless Legs Syndrome (RLS) patients to 35 days of Enhanced External Counter pulsation (EECP)

Patient #	Age and sex	Family history of RLS	Length of RLS sx	Diabetic peripheral Neuropathy and Rx result	Pre-RX IRLS Score	IRLS after 35 day Of EECP	IRLS at 3–6 month after Rx	IRLS at 1 year after Rx	Meds for RLS or Neuropathy
# 1	64 M	No	23 years	Yes better	26	0	–	0	None
# 2	55 M	No	5 years	Yes better	27	0	–	–	None
# 3	74 M	No	9 years	Yes Not better	28	0	0	20	Gabapentin 1500 mg/d
# 4	61 M	No	Since young adult	No	23	4	0	6	None
# 5	80 F	Yes	20 years	No	34	5	10	–	None
# 6	63 M	No	5 years	Yes better	35	27	–	17	Gabapentin 900 mg/d
Avg. and *P* value					28.8	6 ($P<0.03$)	3.3	10.8	

Treatment response was determined using the International Restless Legs Syndrome Study Group Rating Scale for RLS (the IRLS).

In summary, this patient had moderate to severe RLS and diabetic peripheral neuropathy. EECP treatment resulted in total disappearance of RLS symptoms, which is sustained for 1 year after treatment. This is also confirmed by the objective measurement with the IRLS. The patient also noticed subjective improvement in his appreciation of pain and light touch in the legs.

2.2. Patient 4

This is a 61-year-old man who has had symptoms of RLS since young adulthood. He meets criteria for RLS by the IRLSSG [16]. His symptoms are characterized by leg discomfort, which results in a need to move. His symptoms are worse at night, worse sitting or lying down and he experiences significant relief by moving around. Prior to EECP his symptoms occurred 6–7 times per week and lasted about 3–8 h per night, which resulted in significant sleep disruption. He sometimes experiences multiple twitches or involuntary jerking of the legs while sitting or lying down when awake and during sleep. He has never been previously diagnosed with RLS. There is no family history of RLS.

He has coronary artery disease and stents were placed 3 years ago. He underwent diagnostic cardiac catheterization in 2002 because of continued symptoms of angina. He was found to have total occlusion of the marginal branch and its stent. There were new 50% lesions in the diagonal and the right coronary arteries. The other three stents were widely patent. He also has a past medical history of colon cancer, which is currently inactive. During the entire course of treatment he has not been on any medications to improve his RLS symptoms.

Prior to EECP 1 year ago his IRLS score was 23, indicating moderate to severe RLS [17,18]. After 35 days of EECP treatment his IRLS score decreased to 4, which indicates insignificant RLS as well as marked symptomatic improvement. Six months after completion of EECP his IRLS score dropped to 0 and he was totally asymptomatic for the whole 6-month period. However, a year after EECP his symptoms have begun to recur with an IRLS score of 6. The patient has noticed minimal return of symptoms over the last 2–3 months.

One year after EECP the patient's neurological examination was normal. There is no weakness. Pinprick, vibration and position sense were within normal limits. Muscle stretch reflexes were also normal in both lower and upper extremities.

In summary, this patient has moderate to severe RLS. There was complete resolution of RLS symptoms up to a year after EECP treatment, at which point there was a gradual return of mild RLS symptoms.

2.3. Patient 5

This is an 80-year-old woman who has had symptoms of RLS for 20 years. She meets criteria for RLS according to the IRLSSG [16]. Her symptoms are characterized by leg discomfort, which she describes as a creepy, crawly feeling resulting in a need to move. When she has experienced her symptoms, she could not stay still; she tossed and turned in bed and walked the floor in the middle of the night. Her symptoms were worse at night, worse sitting or lying down and she experienced significant relief by walking around. Prior to EECP her symptoms occurred 6–7 times per week and lasted about 8 or more hours per day, which resulted in significant sleep disruption. She is not aware of any involuntary twitches of her legs either awake or in sleep. There is a strong family history of RLS. Her mother had symptoms of RLS and her son currently has RLS symptoms.

This patient has coronary artery disease, hypertension and hypercholesterolemia. She had a myocardial infarction 2 years ago with subsequent two-vessel coronary bypass grafting and stent placement. Six months prior to EECP the patient experienced pressure under the chest and shortness of breath. After EECP her chest pressure improved, but her shortness of breath remained the same. She was not on any medications known to improve her RLS symptoms throughout the course of EECP treatment.

Her IRLS score prior to EECP was 34, which indicates severe to very severe RLS [17,18]. This score decreased to 5 at the completion of 35 days of EECP treatment. This indicates clinically insignificant RLS. Three months after completing the EECP treatment her IRLS score had increased to 10, which indicated return of mild RLS. Prior to EECP the patient could hardly sleep at night and had to walk the floor most of the nights. These walking episodes lasted at least an hour. She also experienced severe symptoms not only at night, but during the day as well.

Six months after completion of EECP treatment she experiences the RLS symptoms only 1 h per night, one to two nights per week. She does not have any daytime symptoms now. Currently, when she needs to get up and walk around in the middle of the night she only has to do this for 5–10 min and can rapidly go back to bed.

Six months after EECP treatment her neurological examination including muscle strength, tone, stretch reflexes and sensation was normal.

In summary, this is an 80-year-old woman with long-standing severe to very severe RLS who experienced almost total resolution of her RLS symptoms with EECP. This benefit has been maintained for up to 6 months post-EECP treatment.

2.4. Patient 6

This is a 63-year-old man who has had symptoms of RLS for 5 years. He meets criteria for RLS according to the IRLSSG [16]. His symptoms are characterized by creepy, crawly sensations of the legs and the need to move. His symptoms are worse at night, worse sitting or lying down to watch television in the evenings around 4–8 pm, and he experiences significant relief by moving the legs. He does

not walk around secondary to hip pain. Prior to EECP his symptoms occurred 6–7 times per week and lasted about 8 h or more per day, which resulted in significant sleep disruption. He is not aware of any twitching or involuntary jerking of the legs either awake or sleeping. He has never been diagnosed with RLS in the past. There is no family history of RLS.

This patient has a history of insulin-dependant diabetes mellitus, hypertension, hypercholesterolemia, coronary artery disease and congestive heart failure. About 2 years ago he underwent aorto-coronary bypass surgery with a left internal mammary artery graft to the left anterior descending artery. He also complained of chest pain and shortness of breath prior to coronary bypass graft. His chest pain improved, but he continued to have shortness of breath after the bypass. After the EECP treatment his shortness of breath also improved significantly.

He was on a stable dosage of gabapentin (Neurontin) 900 mg per day for Neuropathy pain prior to entry into the study. His dose remained constant throughout the study.

Prior to EECP 1 year ago his IRLS score was 35, indicating severe to very severe RLS [17,18]. After 35 days of EECP treatment, his score decreased only to 27, which is still a moderately severe RLS score. He did not have any improvement in his urge to move his legs. At completion of EECP his symptoms still occurred 6–7 times per week, but only lasted for 1–3 h per night. A year after EECP his symptoms are still present, but they are less bothersome to him at the time he is actually having the symptoms and last for 3–8 h per night about 6–7 times per week. His IRLS score has decreased only to 17. The patient felt a small amount of improvement in his RLS symptoms after a year.

Prior to EECP the patient reported complete loss of sensation below the knees in both legs for three years. After EECP treatment he began to perceive sensation in his legs, which he appreciated as a return of a feeling of tingling in his toes. Prior to EECP he could not feel his toes moving and now after treatment he can feel his toes moving again.

After EECP treatment on neurological examination there is no weakness of the legs or arms. Both legs have decreased sensation to pinprick in a stocking distribution. Pinprick is normal in upper extremities. Vibration is decreased distally in both upper and lower extremities, with toes being more affected than ankles and ankles being more affected than knees. Position sense is mildly impaired in the toes, but within normal limits in the fingers. Bilateral ankle jerks are decreased. Upper extremity reflexes are normal. These findings are suggestive of significant diabetic peripheral neuropathy. There is a subjective return of sensation to the lower extremities after the course of EECP treatment.

In summary, this is a 63-year-old man with a history of RLS and significant diabetic peripheral neuropathy. He experienced subjective improvement in his diabetic peripheral neuropathy, but only mild objective and subjective improvement in his RLS after EECP treatment.

3. Methods

We identified six patients (1F, 5M, ages 55–80) who were candidates for EECP treatment, who also had RLS by IRLSSG criteria [16], and who were not previously treated for RLS. Five patients had refractory angina and one had congestive heart failure. None had leg edema. We screened all of our patients for abdominal aortic aneurysm and deep vein thrombosis with abdominal ultrasound and duplex ultrasound of the legs.

EECP was administered for an hour a day Monday through Friday for 7 weeks for a total of 35 days. EECP involves inflation and deflation of three sets of compressive cuffs wrapped around the patient's calves, lower thighs and upper thighs. During diastole the cuffs inflate sequentially from the calves to the upper thighs and buttocks to compress the vascular beds of the legs, increasing venous return to the heart and increasing diastolic aortic pressure and coronary perfusion pressure. EECP was administered in the recumbent position for the hour between 9 am and 4 pm when, except for the added burden of recumbency, RLS symptoms would be expected to be minimal.

All patients were given the International RLS Study Group rating scale for RLS (the IRLS) [17,18] before and immediately after 35 days of EECP treatment. Three patients completed the RLS rating scale 4–5 months after EECP treatment. We also administered the IRLS to four patients after about a year of completing the EECP treatment.

4. Results

Table 1 gives the summary of the results. Among the six RLS patients, four had diabetic peripheral neuropathy by examination and two did not have diabetes or signs of peripheral neuropathy. Of the four patients with diabetic peripheral neuropathy none had a family history of RLS. Of the two patients without diabetic peripheral neuropathy one had a family history of RLS. Two patients were on stable dosages of gabapentin for back pain and neuropathy prior to entry into study and the dose remained stable throughout the study (patients 3 and 6 in Table 1).

Five of the six patients reported improved sleep and RLS symptoms (Table 1). The average IRLS rating scale score before treatment was 28.83 (23–35) and after 35 days of EECP was 6.0 (0–27) ($P < 0.03$ by Wilcoxon signed rank) (Table 1). Three of these RLS patients had 100% symptomatic improvement with a moderate to severe initial IRLS score of 26, 27 and 28 (patients 1–3 in Table 1) that decreased to 0 after the 35 days of EECP treatment and they were totally asymptomatic for RLS. They had symptoms present for 23, 5 and 9 years, respectively, that occurred 4–5 days per week for 1–3 h per night. The IRLS scores of the other two patients (patients 4 and 5 in Table 1) went from 23 and 34 to 4 and 5, respectively. Patient 4 had had RLS symptoms since young adulthood and patient 5 had had RLS

symptoms for 20 years. Prior to EECP they were experiencing symptoms 6–7 days per week for 3–8 h per day. Patient 6 did not improve.

Long-term follow-up was available for three patients at 3–6 months, which showed sustained improvement in all three (patient 3–5 in Table 1). Long-term follow-up was available in four patients at 1 year, which showed sustained improvement in two (patients 1 and 4 in Table 1).

Gabapentin is sometimes used to treat RLS, but paradoxically the two patients on gabapentin (patients 3 and 6 in Table 1) showed the least long-term improvement in RLS symptoms. No other patients were on any other medications known to improve the symptoms of RLS, such as dopaminergic agents, opiates or benzodiazepines.

Of the four patients with diabetic peripheral neuropathy (patients 1–3 and 6 in Table 1), 3 reported subjective improvement in their peripheral neuropathic symptoms, such as an improvement in numbness in their feet and the ability to feel their feet on the floor (patients 1, 2 and 6 in Table 1).

At first glance there seems to be a possible correlation between the improvement in RLS symptoms and improvement in neuropathic symptoms. Two of the three patients who reported improvement in diabetic peripheral neuropathy (patients 1 and 2) also showed a marked improvement in RLS symptoms and score (Table 1). Patient 3 who reported no improvement in diabetic peripheral neuropathy at 1-year follow-up also showed a higher RLS rating score at that time with return of RLS symptoms. However, the two patients without diabetic peripheral neuropathy (patients 4 and 5) also showed marked improvement in RLS symptoms after EECP.

5. Discussion

This preliminary study shows that EECP is an effective treatment for RLS in patients with and without diabetic peripheral neuropathy. The IRLS scores showed a 22.8-point drop after EECP, which is far more than the placebo response of an eight-point drop seen in trials of pharmacotherapeutic agents for RLS. The improvement in some cases also lasts for months after the last treatment. In this way EECP is unique and unlike pharmacotherapy, which requires continuous daily treatment.

We screened all of our patients for abdominal aortic aneurysm and deep vein thrombosis and if these conditions are ruled out, EECP is found to be safe in this patient population [19]. Linnemeier et al. [19] studied 1532 patients, 43% of whom had diabetes mellitus at baseline, and 79% of whom completed EECP. Despite a high-risk profile among the diabetic group in this study, 1-year mortality was similar to a coronary intervention registry population [19]. Arora et al. [20] reported a multi-center, prospective, randomized, blinded, controlled trial which was conducted in seven university hospitals in 139 outpatients who underwent EECP and it was relatively well tolerated and free of limiting side effects in most patients.

We did not have electromyography (EMG) or nerve conduction studies prior to and after EECP in the diabetic patients to objectively assess any improvement in diabetic peripheral neuropathy. However, the symptoms of peripheral neuropathy apparently improved subjectively in 75% of our diabetic patients. This is possibly due to increased vascular flow to the lower limbs after EECP, which would presumably improve the function in the peripheral nerves.

Our results are clearly preliminary. The IRLS only rates symptoms in the week before the scale is given. However, subjective reports from many of our patients who indicate improvement lasting up to a year are also encouraging. We need a large number of patients in a double-blind study with accompanying polysomnography, actigraphy, nerve conduction studies and EMG to draw further conclusions. EECP is a safe treatment [19], and it can be considered also for patients without cardiac disease.

Our results are true independent of the presence or absence of cardiac disease since some of our patients had had RLS since young adulthood, long before the onset of heart disease. Our results are due either to increased collateral circulation, neurohumoral effects or to both [14,15]. Decreased blood flow to the legs and pelvic area has been implicated directly in the pathogenesis of RLS through the mechanisms of lumbar spinal stenosis [9] or varicose veins [10]. However, we cannot exclude the possibility that the results may be due to peripheral sensory modulation of spinal cord or brainstem circuitry, with a mechanism similar to that seen with acupuncture or transcutaneous neural stimulator units rather than to changes in vasculature.

EECP works by increasing blood flow, and it is therefore logical that it may help in improving the symptoms of RLS, if the vascular hypothesis for RLS is true. It is obvious, however, that even if this hypothesis is true that the peripheral or central nervous system must be implicated, at least secondarily, in order for patients to appreciate the abnormal sensation that RLS patients experience in the legs. In this sense, we would favor the reformulation of the hypothesis from ‘Vascular’ to ‘Vascular Neurologic’.

Decreased blood flow to the central or peripheral nervous system may be one of many discrete mechanisms that trigger RLS with other examples being peripheral neuropathy and radiculopathy. Increasing blood flow to the nervous system by EECP treatment may result in an increased supply of needed nutrients to the nervous system, such as iron and magnesium, which have been previously found to be deficient in RLS [21,22].

References

[1] Coccagna G, Vetrugno R, Lombardi C, Provini F. Restless legs syndrome: an historical note. Sleep Med 2004;5:279–83.
[2] Allison FG. Obscure pains in the chest, back or limbs. Can Med Assoc J 1943;48:36–8.

[3] Ekbom KA. Asthenia crurum paraesthetica ('Irritable legs'). New syndrome consisting of weakness, sensation of cold and nocturnal paresthesia in legs, responding to certain extent to treatment with Priscol and Doryl; note on paresthesia in general. Acta Med Scand 1944;118:197–209.
[4] Ekbom KA. Restless legs: clinical study of hitherto overlooked disease in legs characterized by peculiar paresthesia ('Anxietas tibiarum'), pain and weakness and occurring in two main forms, asthenia crurum paresthetica and asthenia crurum dolorosa; short review of paresthesias in general. Acta Med Scand 1945;158: 1–123.
[5] Bonduelle M. Syndrome des jambs sans repos. Paresthesie agitante nocturne des members inferieurs. Rev Rhumatisme 1947; 14:188–9.
[6] Bondule M. Paresthesthesie agitante nocturne des members inferieurs et impatiences. Presse Medicale 1952;60:62–4.
[7] Bondulle M, Jolivet B. Les impatiences. Bull Med 1953;12:316–8.
[8] Jolivet B. Paresthesies agitantes nocturnes des members inferieures. Impatiences. These de paris: Imprimerie R Foulon; 1953.
[9] LaBan MM, Viola SL, Femminineo AF, Taylor RS. Restless legs syndrome associated with diminished cardiopulmonary compliance and lumbar spinal stenosis—a motor concomitant of Vesper's curse. Arch Phys Med Rehabil 1990;71:384–8.
[10] Kanter AH. The effect of sclerotherapy on restless legs syndrome. Dermatol Surg 1995;21:328–32.
[11] Michaels AD, Linnemeier G, Soran D, et al. Two-year outcomes after enhanced external counter pulsation for stable angina pectoris (from the International EECP Patient Registry (IEPR). Am J Cardiol 2004;93:461–4.
[12] Soran O. A new treatment modality in heart failure enhanced external counter pulsation (EECP). Cardiol Rev 2004;12(1):15–20.
[13] Froschermaier SE, Werner D, Leike S, et al. Enhanced external counter pulsation as a new treatment modality for patients with erectile dysfunction. Urol Int 1998;61(3):168–71.
[14] Barsnew GW. Enhanced external counter pulsation in unrevascularizable patient. Curr Interven Cardiol Rep 2001;3(1):37–43.
[15] Feldman AM. Enhanced external counter pulsation: mechanism of action. Clin Cardiol 2002;25(12 Suppl 2):1111–5.
[16] Allen RP, Pitchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003;4:101–19.
[17] Walters AS. The international restless legs syndrome study group validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[18] Hening WA, Allen RP. Restless legs syndrome(RLS): the continuing development of diagnostic standards and severity measures. Sleep Med 2003;4:95–7.
[19] Linnemeier G, Rutter MK, Barsness G, Kennard E, Nesto R. Enhanced external counter pulsation for the relief of angina in patients with diabetes: safety, efficacy and one year clinical outcomes. Am Heart J 2003;146:453–7.
[20] Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counter pulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999;28:1140–6.
[21] Sun EF, Chen CA, Ho G, et al. Iron and the restless legs syndrome. Sleep 1998;21:371–7.
[22] Popoviciu L, Asgian B, Delast-Popoviciu D, Alexandrescu A, et al. EEG clinical electromyographic and polysomnographic studies in restless legs syndrome caused by magnesium deficiency. Rom J Neurol Psychiatry 1993;31(1):55–61.