Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease)

Aaro V. Salminen, MSc
Ville Rimpilä, MSc
Olli Polo, MD, PhD

Correspondence to
Aaro V. Salminen:
aaro.salminen@unesta.fi

ABSTRACT

Objective: A case-control study to measure oxygen and carbon dioxide partial pressures in the legs in order to assess the involvement of peripheral hypoxia or hypercapnia in the pathogenesis of restless legs syndrome (RLS).

Methods: RLS severity was assessed with a standard questionnaire. Suggested immobilization tests were performed twice in 15 patients with RLS and 14 healthy controls. Patients with RLS participated in the tests with and without pramipexole medication. During the tests, peripheral oxygen and carbon dioxide partial pressures were measured noninvasively on the skin of the legs and the chest.

Results: During immobilization, the patients with RLS had lower partial pressure of oxygen in their legs (5.54 vs 7.19 kPa, $p < 0.01$) but not on the chest (8.75 vs 8.20 kPa, $p = 0.355$). More severe RLS correlated with high chest-to-foot oxygen gradient ($\rho = 0.692$, $p < 0.01$). Carbon dioxide levels did not differ between the groups. Pramipexole corrected the peripheral hypoxia toward the levels observed in the controls (from 5.54 to 6.65 kPa, $p < 0.05$).

Conclusions: Peripheral hypoxia is associated with the appearance of RLS symptoms. Strong correlation with RLS severity suggests a close pathophysiologic link between peripheral hypoxia and the symptoms of RLS. This is further supported by the simultaneous reversal of hypoxia and discomfort by dopaminergic treatment. *Neurology*® 2014;82:1856–1861

GLOSSARY

IRLSSG = International Restless Legs Syndrome Study Group; **ptco$_2$** = partial pressure of carbon dioxide; **pto$_2$** = partial pressure of oxygen; **RLS** = restless legs syndrome; **Sao$_2$** = arterial oxyhemoglobin saturation; **SIT** = suggested immobilization test; **tcco$_2$** = transcutaneous carbon dioxide; **tco$_2$** = transcutaneous oxygen.

Restless legs syndrome (RLS) is characterized by paresthesia typically occurring at rest. The uncomfortable feeling is almost exclusively present in the most peripheral part of the body, the legs.[1] During immobilization, the discomfort in the legs increases in a crescendo pattern[2] until relieved by leg movement. The symptoms are effectively relieved by dopaminergic treatment.[3]

The origin of RLS is currently debated. Recently, several studies have found evidence for abnormal peripheral microvasculature in patients with RLS, originally suggested by RLS pioneer Karl-Axel Ekbom in 1945.[4] Microvascular abnormalities have also been suggested by blood flow studies,[5] as well as by genetic studies demonstrating the possible involvement of nitric oxide.[6] Vascular endothelial growth factor upregulation[7] and capillary tortuosity[8] in the legs of patients with RLS provide indirect evidence for peripheral hypoxia. However, hypoxia has not been demonstrated to be present in patients with RLS. Because hypoxic pathways may be activated by other mechanisms in normoxic conditions,[9] direct measurement of oxygen is needed to determine whether hypoxia has a role in the activation of these pathways.

The partial pressures of oxygen and carbon dioxide (ptO_2 and $ptCO_2$) in tissue are affected by blood perfusion through the microvasculature, in addition to arterial oxygen supply. Therefore, we hypothesized that the suggested microvascular abnormalities would result in abnormal ptO_2 and $ptCO_2$ levels in patients with RLS during the symptomatic period. In this study, we used transcutaneous measurements to evaluate the oxygen and carbon dioxide levels in the peripheral tissues in patients with RLS with and without dopaminergic therapy.

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From the University of Tampere (A.V.S., V.R., O.P.), School of Medicine; Unesta Research Centre (A.V.S., V.R., O.P.), Tampere; and Department of Respiratory Medicine (O.P.), Tampere University Hospital, Finland.

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METHODS **Subjects.** A total of 29 subjects were included in the study: 15 patients previously diagnosed with idiopathic RLS and currently treated with pramipexole, and 14 age- and sex-matched controls without RLS symptoms in the subject or in close family. The diagnosis of RLS was confirmed by an experienced specialist in sleep medicine and RLS (author O.P.) according to the standard diagnostic criteria.[10] All subjects with significant other medical conditions were excluded. All subjects in the RLS group had plasma ferritin above 15 μg/L in previous measurements.

Procedures. Pramipexole medication of the patients with RLS was discontinued at least 2 weeks before the start of the study. After 2 weeks off pramipexole, RLS severity was evaluated with the standard International RLS Study Group (IRLSSG) scale.[11] Two sessions of suggested immobilization tests (SITs) were performed in a sleep laboratory environment, 2 and 4 hours before bedtime. SIT is a standardized test to objectively assess the symptoms of RLS.[12] Multiple SITs are recommended for accurate evaluation of the symptoms.[13] The SIT sessions lasted for 60 minutes, during which the patients were asked to rest in a bed in a semisitting position and to avoid moving their legs voluntarily. Neither sleeping nor talking, reading, or any other stimulatory activity was allowed during the tests. Two days after the first SITs, pramipexole medication was recontinued at the effective dose the patient was taking before the discontinuation (dose ranging from 0.25 to 0.50 mg). During the second evening on pramipexole, the patients returned to the study center for 2 consecutive SIT sessions. Control subjects did not take any dopaminergic medication.

During the SITs, arterial oxyhemoglobin saturation (Sa_{O_2}) was measured from the second toe of the foot. Transcutaneous carbon dioxide and oxygen (tc_{CO_2} and tc_{O_2}) signals were simultaneously recorded both from the chest and from the sole of the foot with TCM4 devices paired with Severinghaus type E5280 sensors (Radiometer, Copenhagen, Denmark). Severinghaus correction and metabolic correction factors were disabled from the devices in order to measure the gas partial pressures in the tissues instead of estimating the arterial values. Chest-to-foot gradient of the oxygen and carbon dioxide levels (e.g., pt_{O_2} gradient = pt_{O_2}[chest] − pt_{O_2}[foot]) were calculated to estimate the distribution of the gases between the central and peripheral parts of the body. During the SIT, subjects were prompted every 5 minutes to record the current level of leg discomfort on a scale ranging from no discomfort (value 0) to maximal discomfort (value 10). At each time point, the values of tc_{CO_2}, tc_{O_2}, and Sa_{O_2} measurements were recorded. A mean value of these parameters in the 2 SITs was used in the analyses.

Statistical methods. We tested 3 primary hypotheses for both the oxygen and carbon dioxide measurements: (1) peripheral partial pressures are altered in patients with RLS compared with controls, (2) the measured partial pressures show correlation with IRLSSG scale score of RLS severity, and (3) peripheral levels are modified by pramipexole treatment in patients with RLS. Carbon dioxide and oxygen values between the patients and individually matched controls were compared at each time point during the SIT with 2-tailed Mann-Whitney test. Measurements in patients with RLS with and without medication were compared with 2-tailed Wilcoxon signed-rank test. Correlations were evaluated with Spearman rank correlation coefficient.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethical committee (Pirkanmaa Hospital District, Tampere, Finland). All patients signed informed consent before any study procedures.

RESULTS The patient and control subject groups were matched for age and sex. The mean ages were 57.1 and 56.6 years, respectively. Seven of 15 patients and 6 of 14 controls were women. All patients had been previously diagnosed with idiopathic RLS. The mean RLS severity after the discontinuation of pramipexole medication was 23.7 in the RLS patient group. One subject in each subject group had to be excluded because of insufficient quality of the transcutaneous recording. Patients with RLS who did not have significant RLS symptoms (IRLSSG scale severity <15, n = 3) 2 weeks after discontinuation of pramipexole were excluded from the analyses comparing patients with RLS and controls, but not from the analysis of correlation between RLS severity and measured values.

The mean values of subjective discomfort, pt_{O_2}, pt_{CO_2}, and Sa_{O_2} levels during SIT in the different patient groups are presented in the table. The levels of pt_{O_2} and pt_{CO_2} on the chest did not differ between the patient and control groups. In contrast, patients with RLS had lower oxygen levels in their legs during the SIT compared with controls. Also the chest-to-foot pt_{O_2} gradient differed significantly between the 2 groups. There was no difference between the groups in the measurements of carbon dioxide or Sa_{O_2}.

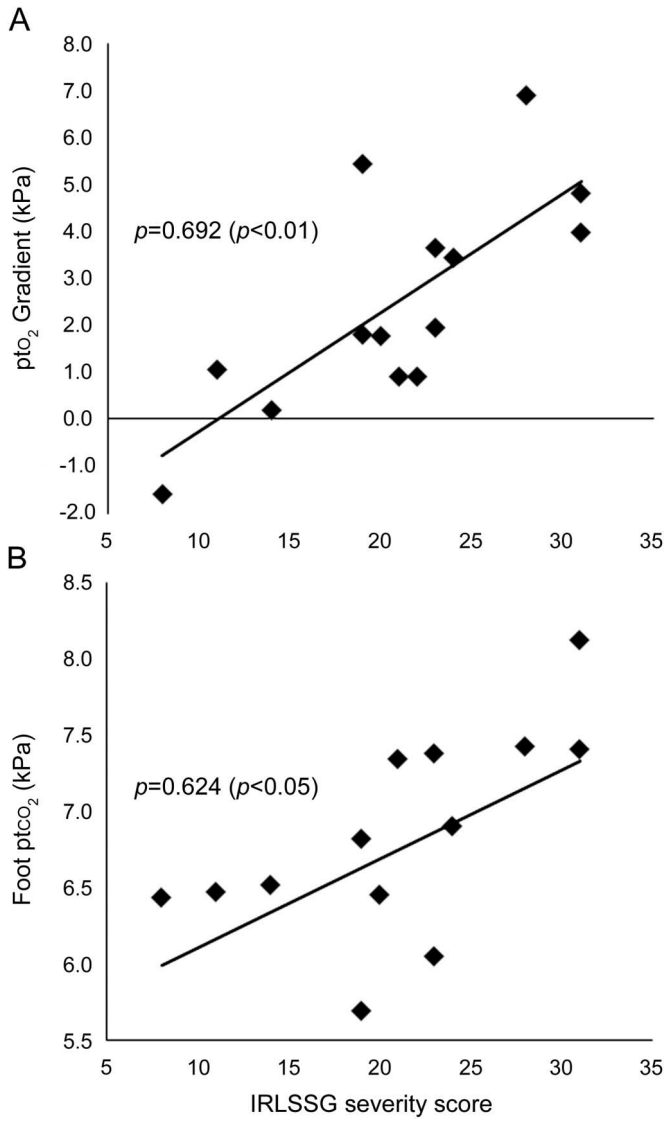
The pt_{O_2} gradient had a strong, statistically significant correlation with RLS severity: the more severe RLS the patient had, the greater the difference in pt_{O_2} was between the chest and the periphery (Spearman correlation $\rho = 0.692$, $p < 0.01$). Moreover, the more serious cases of RLS also had higher levels of absolute pt_{CO_2} in their legs ($\rho = 0.624$, $p < 0.05$). Scatter plots of these parameters, plotted against RLS severity, are displayed in figure 1. Other measurements of oxygen and carbon dioxide did not correlate significantly with RLS severity in our patient population (foot pt_{O_2}: $\rho = -0.404$, $p = 0.152$; and pt_{CO_2} gradient: $\rho = -0.463$, $p = 0.095$).

Table Mean values of discomfort and partial pressures of oxygen and carbon dioxide during SIT

	RLS	Control	p	RLS (PPX)	p
Discomfort	4.2	0.1[a]	<0.001	1.6[a]	<0.001
Foot pt_{O_2}, kPa	5.54	7.19[b]	<0.01	6.65[c]	<0.05
Chest pt_{O_2}, kPa	8.75	8.20	0.355	7.86	0.156
pt_{O_2} gradient, kPa	3.22	0.93[b]	<0.01	1.21[c]	<0.05
Foot $ptco_2$, kPa	6.82	6.92	0.955	7.24	0.173
Chest $ptco_2$, kPa	6.69	6.80	0.710	7.16	0.117
$ptco_2$ gradient, kPa	−0.12	−0.11	0.691	−0.04	0.594
Sao_2	97.7%	97.7%	0.955	97.5%	0.477

Abbreviations: PPX = pramipexole; RLS = restless legs syndrome; Sa_{O_2} = arterial oxyhemoglobin saturation; SIT = suggested immobilization test.
RLS and control values represent the mean. The subjective discomfort was assessed with a scale ranging from 0 to 10. The measurements were performed in patients with RLS on 2 occasions (on and off PPX). In healthy controls, the values are means of 4 SIT sessions measured during 2 evenings. The p values are shown in comparison to drug-free patients with RLS.
[a] $p < 0.001$.
[b] $p < 0.01$.
[c] $p < 0.05$.

Figure 1 Linear regression of the chest-to-foot ptO_2 gradient and foot $ptcO_2$ vs restless legs syndrome severity



Values of the chest-to-foot gradient of partial pressure of oxygen (ptO_2, A) and foot partial pressure of carbon dioxide ($ptcO_2$, B) plotted against International Restless Legs Syndrome Study Group (IRLSSG) severity scale scores.

The recontinuation of pramipexole did not have an effect on ptO_2 on the chest but increased the mean foot ptO_2 and therefore decreased ptO_2 gradient during SIT (table). Carbon dioxide levels or distribution did not change with treatment.

Figure 2 displays the evolution of oxygen and carbon dioxide measurements, as well as the subjective discomfort, during the SIT in each patient population. Although the effects of pramipexole on foot $ptCO_2$ were not significant when comparing mean levels during SIT, the effect was significant at several individual time points during the test, especially toward the end of the immobilization. The effect of pramipexole on foot ptO_2 was not statistically significant at some time points.

In the most severe of our RLS cases (n = 3, IRLSSG scale severity ranging from 28 to 31), the patterns of leg movements and ptO_2 measured on the foot were closely connected during SIT (example in figure 3): the ptO_2 was decreasing spontaneously when legs were still and relaxed. When a movement occurred, the oxygen level increased momentarily and started to decrease again after relaxation. This pattern was not observed in cases of mild to moderate RLS.

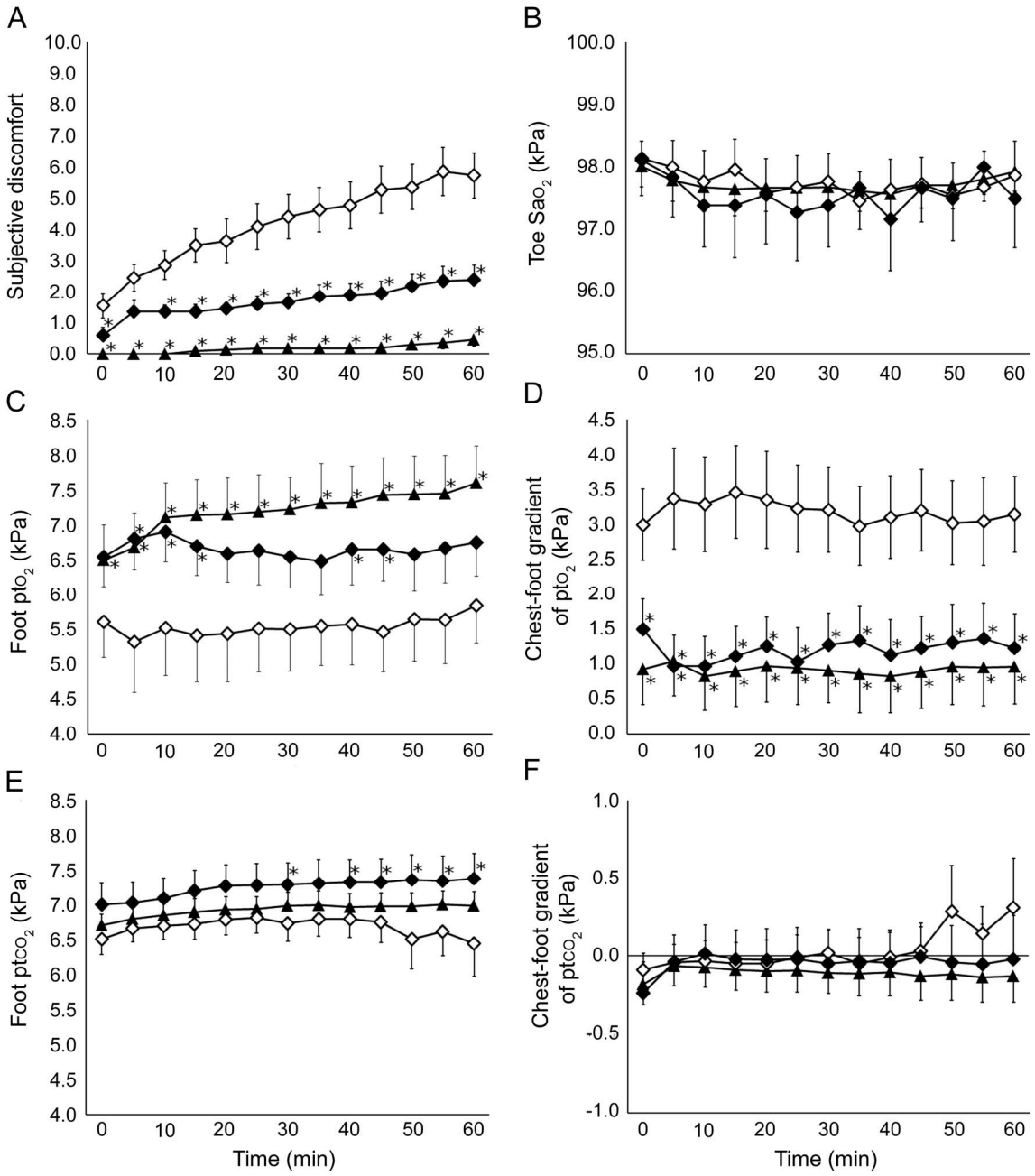
DISCUSSION Most previous studies on RLS have focused on the CNS. Our data add to the emerging body of evidence supporting the hypothesis that peripheral phenomena also contribute to the pathophysiology of RLS. The most important new finding of our study is the demonstration of peripheral hypoxia in patients with RLS and its close relation to RLS severity, supporting the hypothesis of microvascular abnormalities in RLS. In addition, the restoration of peripheral oxygenation with pramipexole, the first-line therapy for RLS,[14] is in agreement with the thinking that peripheral hypoxia may not only be involved in symptom generation, but its correction may also mediate some of the treatment effect. These findings are consistent with our hypothesis that peripheral systems are involved in RLS pathophysiology.

It is unlikely that the lowered ptO_2, observed in patients with RLS, could have been caused by changes in partial pressure of arterial oxygen, because no changes were observed in the peripheral SaO_2. To control for potential bias from individual systemic differences in skin oxygenation, ptO_2 and $ptCO_2$ were measured simultaneously on the skin of the chest. The chest measurements showed no difference between the 2 patient groups. These findings demonstrate that in RLS, lowered oxygen levels are specific to the peripheral parts of the body and are not a systemic phenomenon.

There was a strong positive correlation between the severity of RLS symptoms when off pramipexole and the chest-to-foot gradient of tissue oxygen. This suggests that peripheral hypoxia is not only a circumstantial finding during the moment of immobilization but also a feature closely related to the degree of subjective RLS complaint. The finding supports the involvement of hypoxia in RLS pathophysiology either as a primary trigger or a closely related secondary phenomenon.

The low ptO_2 in the extremities, characteristic of RLS, was corrected with a standard dose of pramipexole. The treatment simultaneously resolved the RLS discomfort. The mechanism of action of dopamine agonists in RLS is generally thought to be in the CNS,[15] although the exact site of action has not yet been identified. Dopamine receptors are present in all parts of the body. In systemic arteries,[16] dopamine is a potent arterial vasodilator,[17] and it enhances blood flow in subcutaneous fat tissue and peripheral skeletal muscles.[18] The redirection of blood flow to the periphery could potentially explain our findings. The fact that pramipexole simultaneously

Figure 2 Development of discomfort, and oxygen and carbon dioxide during SIT



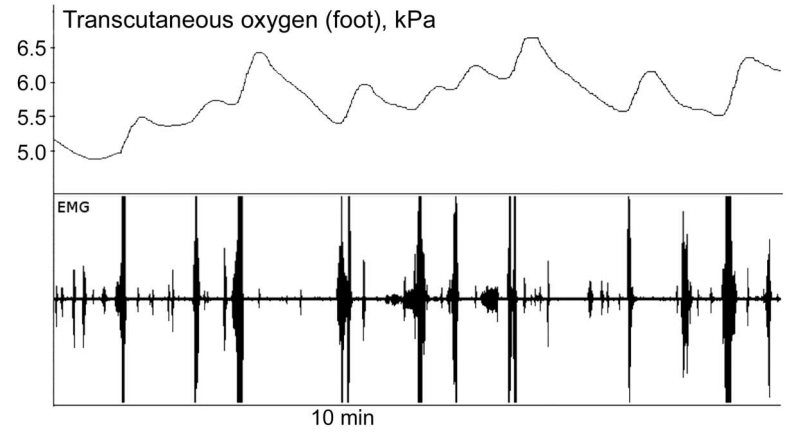
Evolution of subjective discomfort (A), arterial oxyhemoglobin saturation (B), and the foot partial pressures and chest-to-foot gradients of partial pressures of oxygen (pt_{O_2}, C and D) and carbon dioxide (pt_{CO_2}, E and F) during SIT. Subject groups are patients with RLS without therapy (◊), patients with RLS receiving pramipexole (♦), and healthy controls (▲). *$p < 0.05$ compared with the RLS group without therapy. RLS = restless legs syndrome; Sao2 = arterial oxyhemoglobin saturation; SIT = suggested immobilization test.

corrects both subjective discomfort of RLS and peripheral oxygenation, could support the existence of a pathophysiologic link between the 2 phenomena.

At baseline, the pt_{CO_2} levels did not differ significantly between the 2 groups. However, there was a positive correlation between the RLS severity and leg pt_{CO_2} during SIT: higher pt_{CO_2} levels were associated with more severe RLS symptoms. We were expecting to find a difference in the carbon dioxide levels between the groups, reflecting compromised blood flow to the lower limbs. The finding could mean that instead of reduced blood flow, other mechanisms, such as impaired oxygen delivery to peripheral tissues, should also be considered. Pramipexole did not have an effect on the mean pt_{CO_2} in the legs but the effect was significant at single time points toward the end of the SIT. A larger population would be needed to assess this effect in more detail.

In the most severe cases of RLS, the pattern of the fluctuation of tissue oxygen and the appearance of leg movements closely resembled the crescendo pattern of

Figure 3 Movement and pto_2 patterns during SIT



An example of a SIT test recording of a patient with severe restless legs syndrome (IRLSSG scale severity = 31), in whom the pto_2 decreased before and increased after movements. The patient was reporting maximum discomfort (10/10) at the time of the recording. IRLSSG = International Restless Legs Syndrome Study Group; SIT = suggested immobilization test.

the RLS symptoms. The similarity between the pattern of the subjective symptoms and objective measurements provides further evidence for a close connection between the peripheral ptO_2 levels and RLS discomfort.

These findings imply that impaired delivery of oxygen to the periphery has a role in the pathogenesis of RLS. Peripheral hypoxia could be a primary trigger of RLS, irritating peripheral afferent nerves. Afferent signals from muscle nerves have been suggested to be involved in the generation of RLS symptoms by the A11 pathophysiologic model.[19] Irritation of these nerve fibers in the periphery could trigger the uncomfortable sensations through the nociceptive system. Alternatively, hypoxia could be a secondary phenomenon resulting from deficiencies in iron metabolism, often associated with RLS.[20] Impaired iron metabolism has been demonstrated not only in the basal ganglia of the brain but also in blood lymphocytes.[21] Impaired iron metabolism in the peripheral skin tissue could compromise the oxygen uptake to the tissue and explain the current findings. However, more data are needed to forward this hypothesis.

Peripheral hypoxia could explain some of the earlier findings in RLS. It could provide an explanation for the upregulation of vascular endothelial growth factor in the skeletal muscles of the legs in RLS,[7] as well as the capillary tortuosity in the skeletal muscles of the same tissues.[8] Both of these findings are signs of tissue hypoxia. RLS has also been associated with activation of a hypoxia-inducible protein (HIF-1) in substantia nigra,[22] but this hypoxic marker has not been assessed in the peripheral tissues. A central role of hypoxia in the pathogenesis of RLS could also explain the high prevalence of RLS symptoms in disorders associated with hypoxia, such as chronic obstructive pulmonary disease[23] or obstructive sleep apnea.[24] In addition, the possible beneficial use of different compression devices in RLS[25] could be explained by the involvement of peripheral oxygen in RLS pathogenesis.

The simultaneous effect of pramipexole on both the peripheral oxygen levels and RLS symptoms could further support a primary role of hypoxia in RLS pathophysiology. If hypoxia was a primary trigger of RLS symptoms, the correction of peripheral oxygen levels by dopaminergic therapy would efficiently suppress the symptoms. A recent study showed that the cerebral effects of dopaminergic agents are not necessary for their therapeutic effect on periodic leg movements in a patient with complete spinal cord lesion.[26] The data presented here raise the hypothesis that the same could be true in RLS.

In this study, we used the transcutaneous method to assess ptO_2 and $ptCO_2$. Pulse oximetry is the conventional technique to assess oxygenation, measuring SaO_2. The ptO_2 and $ptCO_2$ levels are affected by SaO_2, but also by blood perfusion, and are therefore sensitive to vasoconstriction. Transcutaneous measurements may be used to noninvasively estimate the levels of ptO_2 and $ptCO_2$ in skin tissue.[27] Transcutaneous O_2 is used in the diagnosis of peripheral vascular insufficiency,[28] and agrees well with MRI measurements of oxygen in certain patient groups.[29] Transcutaneous CO_2 is used to evaluate limb ischemia in surgery.[30] Therefore, we believe that tcO_2 and $tcCO_2$ are the most appropriate methods to continuously monitor ptO_2 and $ptCO_2$ in skin.

There are several limitations to the interpretation of our results. Although the tcO_2 method has been shown to correlate with MRI measurements of the oxygen content in underlying muscle tissue,[29] the method remains insufficiently validated in different patient populations. The signal could be affected by various other factors, including vasoconstriction.[31] Interpretation of the signal is therefore difficult and it may not fully translate to ptO_2 of the underlying tissues. Another limitation is that this is the first study to explore the connection between RLS and peripheral oxygen levels, and the results require confirmation in future studies, perhaps in larger patient populations.

Taken together, our data provide a set of findings that increases the evidence for the involvement of peripheral factors in RLS pathophysiology. The findings are consistent in supporting the association of RLS with peripheral hypoxia and provide an explanation for the previously described activation of hypoxic pathways in RLS. Moreover, our data provide a new potential mechanism of action for dopaminergic therapy in suppressing RLS.

AUTHOR CONTRIBUTIONS

Aaro V. Salminen: drafting or revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Ville Rimpilä: drafting or revising the manuscript, study concept or design. Olli Polo: drafting or revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision or coordination.

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DISCLOSURE

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