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Original Article

Effect of Blood Flow Restriction in Low-Intensity Resistance Training of Quadriceps Femoris on Lower Extremity Strength in Patients with Knee Osteoarthritis

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ABSTRACT

Background: Strengthening exercises on the quadriceps muscles can improve the physical function of people with knee OA (KOA). Low-intensity resistance training (LI-RT) with Blood Flow Restriction (BFR) increases muscle strength, equivalent to high-intensity resistance training (HI-RT). However, little is known regarding the effect of BFR exercises on lower extremity strength in patients with KOA measured by 30STS test and the prescriptions are still very diverse. This study aim determine the BFR effect in LI-RT of the quadriceps femoris muscle on lower extremity strength in patients with KOA measured by 30 Seconds Sit to Stand (30STS) test.

Methods: Twenty-eight patients with Kellgren Lawrence grades 2 and 3 KOA. The intervention group (n=14) received LI-RT with BFR, while the control group (n=14) only received LI-RT. Lower extremity strength was measured by 30STS test before and after 6 weeks of exercise.

Results: There was a significant difference in each group's 30STS score before and after training ($p < 0,05$). There was a significantly higher 30STS score after the exercise and the delta value ($p < 0,05$) in the intervention group compared to the control group.

Conclusions: The BFR addition in LI-RT for 6 weeks increases lower extremity strength in patients with KOA.

GRAPHICALABSTRACT

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Introduction

The functional ability of patients with KOA is mostly affected by muscle weakness and poor proprioception function [1]. Quadriceps muscle weakness is a common condition found in patients with KOA, as the quadriceps femoris is a monoarticular muscle and dominated by type II muscle fibers, in which type II muscle fibers are more sensitive to immobilization conditions and will decrease in number with age [1]. Strengthening exercises on the quadriceps muscles can improve the physical function of people with OA. Loads requirement on resistance training recommended by the American College of Sport Medicine (ACSM) is at least 70% of 1 repetition maximum (1 RM) to achieve muscle hypertrophy and increase muscle strength. However, patients with KOA are often unable to exercise at that intensity [2]. Low-intensity resistance training (30-40% 1-RM) for less than four weeks can increase muscle strength through neural adaptation, although there is no evidence of changes in muscle morphology (hypertrophy). It is also safe and more suitable for people who are unable to do HI-RT or with a limited range of motion [3]. In recent years, addition of BFR in LI-RT has become popular because of its positive effect on increasing muscle mass and strength, equivalent to high-intensity exercise. This can be an alternative exercise for patients with KOA who cannot do HI-RT [4, 5]. Exercise with BFR is an exercise with partial occlusion of arterial and venous blood flow for a certain period that cause metabolic accumulation, increasing of growth factor, recruitment of fast twitch muscle fibers, Nitric oxide synthase 1 (NOS-1), and protein synthesis through mammalian target of rapamycin (mTOR) [2]. Quadriceps muscles weakness in KOA causes difficulties in performing basic activities of daily life that require adequate lower extremity strength, such as getting up from a chair or bed. Osteoarthritis Research Society International (OARSI) recommends a physical performance-based test to assess functional abilities in patients with knee OA using the 30STS [6].

Prescriptions of LI-RT combined with BFR are still very diverse and little is known regarding the effect of BFR exercises on lower extremity strength in patients with KOA measured by 30STS test. Therefore, the purpose of this study was to evaluate the effect of LI-RT on the quadriceps femoris combined with BFR on lower extremity strength in patients with KOA measured by the 30STS test.

Materials and Methods

This research was conducted at Physical Medicine and Rehabilitation Outpatient Clinic of RSUD Dr. Soetomo Surabaya from January to March 2023. This research has received a certificate of ethical eligibility from the Health Research Ethics Committee of RSUD Dr. Soetomo Surabaya with no. 0544/KEPK/XII/2023.

Total subject of this study was 28 participants (5 males and 23 females) diagnosed with Kellgren Lawrence grade 2 and 3 unilateral or bilateral KOA. All participants divided into two groups, each group consisting of 14 participants. KOA diagnosis was confirmed on the basis of medical history, clinical symptoms, physical examination, and radiological findings as per ACR recommendations. The inclusion criteria included: (1) Patients with knee OA who were confirmed from the clinical criteria of the American College of Rheumatology and radiologically grade II-III according to the criteria of Kellgren and Lawrence, both unilateral and bilateral. If bilateral, then the leg with the higher pain score (VAS) will be included in the study assessment, (2) Male or female aged over 50-70 years, (3) Do not have cognitive impairment (MoCA-Ina score ≥ 26), (4) Willing to sign the research consent form. Exclusion criteria included: (1) Blood clotting disorders, (2) Deep vein thrombosis, (3) Peripheral arterial disease, (4) Peripheral neuropathy and/or polyneuropathy on lower extremities, (5) Cardiorespiratory disease (ischemic heart disease, heart rhythm disturbances, heart failure, valvular disorders, chronic obstructive pulmonary disease, and asthma), (6) Uncontrolled hypertension, (7) Uncontrolled diabetes Mellitus, (8) Thrombotic stroke, bleeding stroke, and transient ischemic attack, (9) Pain on targeted knee joint and/or surrounding soft tissue with a VAS value > 60 (mm), (10) Currently having or history of lower extremity strengthening exercise program in the last 3 months, (11) Injuries, fractures, operations, or other musculoskeletal diseases in the lower extremities in the last 6 months, (12) Currently in therapy using Statin, chemotherapy treatment, or oral contraception, (13) Balance disorder, and (14) Impaired vision and hearing. The intervention group received LI-RT (30% 1-RM) combined with BFR, while the control group only received LI-RT. The BFR application on the intervention group was on the most proximal part of the thigh on the targeted extremity, with 21 cm width thigh cuff using 50 mmHg pressure. The cuff remains inflated throughout the exercise with maximal time of 10 minutes in each session.

The protocol used on both groups was LI-RT with 30% of 1-RM using Quadriceps Bench Machine, 75 repetitions in each session (divided into 5 sets of 15 repetitions with 1 minute rest between sets) for 6 weeks.

The 30STS score were measured pre-test and post-test (96 hours after the last session).

Participants are asked to perform as many full sitting and standing movements as possible in 30 seconds from a standard height chair (42-45 cm) without arm rest with both arms crossed on the chest. All data were analysed using SPSS statistic 26 (IBM, USA) with several tests: Monte Carlo test, Independent t-test, and paired t-test. The effect size was observed using Cohen's-d formula to elaborate the statistical effect of changes. The significance level was set at less than 0.05.

Table 1: Data on the basic characteristics of research subjects

	Treatment Group (n = 14)	Control Group (n = 14)	P-values
Sex[1]			0.622
Male	3 (21.4%)	2 (14.3%)	
Female	11 (78.6%)	12 (85.7%)	
Age (years) [2]	57.71 ± 5.25	61.42 ± 5.70	0.085
Age Category[1]			0.127
Elderly	8 (57.1%)	4 (28.6%)	
Pre Elderly	6 (42.9%)	10 (71.4%)	
Body Weight (Kilograms)[2]	66.78 ± 13.00	64.71 ± 8.65	0.624
Height (Centimeters)[2]	158.78 ± 7.84	152.57 ± 8.73	0.058
BMI (kg/m2)[2]	26.30 ± 3.99	27.85 ± 2.80	0.243
BMI category			0.964
Normoweight	3 (21.4%)	2 (14.3%)	
Overweight	4 (28.6%)	4 (28.6%)	
ObeseGrade I	6 (42.9%)	7 (50%)	
Obese Grade II	1 (7.1%)	1 (7.1%)	
Knees with OA[1]			0.699
Right	8 (57.1%)	9 (64.3%)	
Left	6 (42.9%)	5 (35.7%)	
Grade OA[1]			0.430
Grade 2	10 (71.4%)	8 (57.1%)	
Grade 3	4 (28.6%)	6 (42.9%)	
Ipaq Pre[1]			0.430
Low	10 (71.4%)	8 (57.1%)	
Moderate	4 (28.6%)	6 (42.9%)	
Comorbid [1]			0.313
No Comorbid	9 (64.3%)	8 (57.1%)	
HT	3 (21.4%)	5 (35.7%)	
DM	2 (14.3%)	0 (0%)	

Results and Discussion

The total number of subjects analyzed was 14 participants in each group. The characteristics of the data presented in Table 1 show that the data are normally distributed in terms of sex, age, weight, height, BMI, genes with OA, OA grade, IPAQ score before treatment, and comorbid diseases.

Values are expressed as 1 amount (percentage) and 2 mean ± standard deviation. The P-value is based on the 1 Chi-square test and 2 Independent t-test. Significant if the p-value < 0.05. Most research subjects were women, 78.6% in the treatment group and 85.7% in the control group. The mean age in the treatment group is 57.71 ± 5.25 years and in the control group61.42 ± 5.70 years. This is consistent with the prevalence of knee OA which is found more in women than men, especially women over 55 [7].

The average BMI of the study subjects was 23-34 kg/m^2, with the highest distribution in the obese grade I, namely 6 subjects in the treatment group and 7 subjects in the control group. This is in accordance with a meta-analysis study conducted by Zeng and Chen (2014) which stated that obesity is a decisive risk factor for knee OA [8]. On the other hand, a study by Widhiyanto *et al.* (2017) states that there is no relationship between BMI and the degree of OA genu. This shows that the degree of genu OA is not only determined by BMI, but also by other factors such as history of knee injury and physical activity [9].

The activity level of the research subjects before treatment was assessed using the IPAQ, showing the predominance of subjects with low physical activity. Shim *et al*. (2018) showed that people with knee OA have lower physical activity than those without knee OA [9].

As many as 14.3% of the subjects in the treatment group were patients with type 2 diabetes mellitus who were controlled, and there were 21.4% of the subjects in the treatment group and 35.7% of the subjects in the control group who had controlled hypertension (p-value= 0.313). This is related to the theory that states that the severity degree and risk of knee OA is not only influenced by age and the excess load that occurs on the knee joint due to obesity, but can also be influenced by metabolic factors such as diabetes mellitus and hypertension which affect vascularization and inflammatory response in the knee joint [10, 11].

The 30STS assessment was carried out in the treatment group before and after weight training with the addition of BFR, as listed in Table 2. After the 30STS data showed normal distribution using the Monte Carlo test, the 30STS data was processed using a Paired t-test. Table 2 indicates an increase in post-test scores (13.21 ± 1.718) compared to pre-test values (9.86 ± 1.231). The paired t-test showed a value of p = 0.000, so there was a significant difference in the 30STS pre-test and post-test values. Effect size measurement using Cohen's d and the results obtained are 2.76 so that the addition of BFR in low-intensity muscle weight training quadriceps femoris for 6 weeks to changes in 30STS values have very considerable strength (d> 1). Therefore, low-intensity weight training for 6 weeks had an impact on the value of the 30STS post-test intervention group. The 30STS test is a method of assessing physical function in patients with knee OA recommended by OARSI. The 30STS test assesses lower extremity strength in older adults living in communities and nursing homes while performing functional tasks. In this study, analysis of lower extremity muscle strength values using the 30STS pre and post-test showed a statistically significant increase in the intervention group (p-value= 0.000) and the control group (p-value= 0.000). The increase in the 30STS value in the treatment group that received the addition of BFR was in line with a study conducted by Clarkson *et al.* (2017), which showed a three times greater increase in the 30STS value in the treatment group that received the BFR addition in walking exercise for 6 weeks [12]. The primary mechanism underlying the effects produced through the application of blood flow restriction during muscle strengthening exercises is metabolic accumulation, which stimulates increased growth factors, increased recruitment of fast twitch muscle fibers, and increased protein synthesis via the mammalian target of rapamycin (mTOR) pathway. In addition, increased Nitric oxide synthase 1 (NOS-1), heat shock protein (HSP), and decreased

Myostatin gene expression were also reported to play a role in the occurrence of muscle hypertrophy and increased muscle strength in training with BFR administration [5]. Increased recruitment of fast twitch muscle fibers, and increased protein synthesis via the mammalian target of the rapamycin (mTOR) pathway. Furthermore, increased Nitric oxide synthase 1 (NOS-1), heat shock protein (HSP), and decreased Myostatin gene expression were reported to play a role in the occurrence of muscle hypertrophy and increased muscle strength in training with BFR administration, increased recruitment of fast twitch muscle fibers, and increased protein synthesis via the mammalian target of the rapamycin (mTOR) pathway. Moreover, increased Nitric oxide synthase 1 (NOS-1), heat shock protein (HSP), and decreased Myostatin gene expression were reported to play a role in the occurrence of muscle hypertrophy and increased muscle strength in training with BFR administration [3, 5]. An increase in the 30STS score, which reflects an increase in lower extremity strength, was also found in the control group, which received LI-RT 30% 1 RM, 75 repetitions each session for 6 weeks without additional of BFR. Increase local muscle strength and endurance can be achieved by giving low to moderate intensity loads (20-60% 1-RM) for three to four sets, 40 to 50 repetitions or more [13]. In the same vein, Tanaka *et al.* (2017) and Zeng *et al.* (2021) stated that training with low-intensity loads (20-40% 1-RM) for less than four weeks was able to increase the muscle strength through neural adaptation even though there is no evidence of changes in muscle morphology (hypertrophy) [3, 8].

The 30STS assessment was carried out in the control group before and after weight training without adding BFR, as provided in Table 3. After the 30STS data showed normal distribution using the Monte Carlo test, the 30STS data was processed using a paired t-test.

Table 2: 30STS different test pre and post-test treatment group

Time	Means±SD	P-value	Effect size
Pre-test	9.86±1.231	0.000	2.76
Post-test	13.21±1.718		

Table 3: 30STS different test pre and post-test control group

Time	Means±SD	P-value	Effect size
Pre-test	8.57±2.243	0.000	2.28
Post-test	10.57±2.311		

Table 3 shows an increase in the post-test value of 10.57±12.34) compared to the pre-test (8, 57±2, 243). The Paired t-test showed a p-value = 0.000, so there was a significant difference in the pre-test and post-test 30STS in the control group. The effect size was measured using Cohen's d. The result was 2.28, thus low-intensity weight training of the Quadriceps Femoris muscle using the same number of sets and repetitions as training using the addition of BFR for 6 weeks to changes in the 30STS value has considerable strength (d>1), resulting in low-intensity weight training for 6 weeks had an impact on the 30STS post-test value of the control group. Both groups showed a positive effect on increasing lower extremity muscle strength. However, the increasing in 30STS post-test scores was significantly higher in the BFR group is in accordance with study by Yasuda which provided the BFR addition to walking exercises at a moderate walking speed (4 km/hour) for 8 weeks in patients with KOA [4]. The increase in the 30STS value, which describes the strength of the lower extremity, is related to the positive effect of adding BFR to LI-RT, which can produce hypertrophy and increase in muscle strength similar to HI-RT through metabolic accumulation, which stimulates increased growth factors, fast twitch muscle fibers recruitment, protein synthesis via the mammalian target of rapamycin (mTOR) pathway, production of Nitric Oxide

Synthase 1 (NOS-1), heat shock protein (HSP), and decreased Myostatin gene expression [5, 14].

There are often several issues in exercise with BFR. The most common concern is the risk of blood coagulation and venous thrombus. Studies by Nakajima *et al.* have confirmed that strengthening exercises with BFR do not increase D-dimer, a marker of intravascular blood clot formation. The cuff used in this study was a cuff with a width of 21 cm, which is in accordance with the literature by Cerquira *et al.* (2021) which states that the recommended cuff width for exercises with BFR in the lower limbs is between 5 cm and 23 cm. The wider the cuff size, the smaller the risk of having blood turbulence that cause clot formation. In addition, a wider cuff size provides lower restrictive pressure, but it is sufficient to provide a metabolic accumulation effect and reduce the risk of clot formation in blood vessels, peripheral nerves compression and discomfort/pain [15].

Furthermore, the risk of blood vessel clot formation is affected by the cuff pressure. Previous studies recommend the BFR pressure between 50-300 mmHg. High cuff pressure can increase the risk of cardiovascular response, the formation of venous thromboembolism, and rhabdomyolysis. In this study, the cuff pressure used was 50 mmHg for all subjects in the BFR group. The researcher anticipates the risk of thromboembolism, but also taking into account that there should be hypertrophic effect and increase in muscle strength that have to be occurred using 50 mmHg. Sumide *et al.* (2009), used 3 different occlusion pressures (50 mmHg, 150 mmHg, and 250 mmHg) showing that a pressure of 50 mmHg gave a significant increase in the maximum torque of the quadriceps muscles with no significant difference with the other 2 groups [16].

Apart from the risk of thromboembolism, another risk that is being a concern in BFR is the risk of muscle damage and prolonged Delayed Onset Muscle Soreness (DOMS). During this study, the DOMS that occurred disappeared within 24 hours after exercise, and there were no prolonged DOMS reported by the subjects. This is in accordance with a study by Brandner *et al.* (2017) which stated that DOMS that occurred after exercise using BFR with a cuff pressure of 50 mmHg was shorter than that of exercise using BFR with a cuff pressure of 130 mmHg, while DOMS in both groups disappeared after 96 hours after practice [15].

The exercise duration in this study was 6 weeks, different from previous studies where the average exercise was 8-12 weeks. However, exercise with a frequency of 2 times per week with high repetitions can increase lower extremity muscle strength. It is in accordance to the theory of increased muscle strength can be caused by neural adaptation that leads to an increase in voluntary muscular activation due to increased motor unit recruitment. The most significant changes occurred in the first 4 weeks of training, in which in the early weeks of training, there were modifications to the structure of muscle fibers and caused an increase in neural activation in which the nervous system recruited more motor units and built muscle strength [13].

A comparison of 30STS post-test scores between groups using the independent t-test is listed in Table 4. There were significant differences between groups in the change in 30STS values after 6 weeks of treatment. The effect size using Cohen's d shows a considerable value (d> 0.8), so adding BFR to low-intensity weight training for 6 weeks enormously impacts the 30STS post-test score of the intervention group compared to the control group.

The results of this study showed that the BFR addition to LI-RT of the quadriceps femoris muscle in patients with knee OA for 6 weeks resulted in a significantly higher change in the 30STS score compared to the control group without BFR (p-value = 0.002). The mean value of the 30STS pre-test in the treatment group was 9.86±1,231 and the control group 8.57±2.243 without any significant difference between the two groups. This shows that people with KOA have a decreased ability to sit to stand from the number of sitting to standing that can be done within 30 seconds according to age. Dobson *et al.* (2013) states that the normal value of 30STS in women over 60 is above 12 times in 30 seconds and in men over 60 is 14 times in 30 seconds [17].

Table 4: Comparison of 30STS post-test values between groups

Group	Means±SD	P-value	Effect size
Treatment	13.21±1.718	0.002	0.996
Control	10.57±2.311		

Table 5: Comparison of the difference in the value of 30STS

Group	Means±SD	P-value	Effect size
Treatment	3.36±1.216	0.002	1.28
Control	2.00±0.877		

The sitting-to-standing process involves two phases. The initial phase is lifting the buttocks (buttock off/seat off), and the second phase is lifting the buttocks from the chair until they stop in a standing position.

The sitting-to-standing movement is a process that includes moving the body's center of mass forward and upward (standing movement), and the upper body segments lean forward to shift the body's center of mass. The base of support changed from a wider base of support at first when sitting (the buttocks, thighs, and feet) to a narrower base of support (the legs) without losing balance. This change from a sitting to a standing position that shifts the body's center of mass requires joint movement and a great force in the hip extensor muscles to fight gravity. The quadriceps femoris muscle is active in transferring loads from the hip joint to the knee joint, directing the ground reaction force backwards, and controlling balance. Patients with KOA tend to compensate when they move from sitting to standing to avoid pain. Patients with OA of the knee experience asymmetric load distribution on the knee that has OA, reduced knee flexion, the body leans to the side of the contralateral knee, which is painless, and the torso is more flexed when moving from sitting to standing. Ineffective knee extension movements due to the strength of the quadriceps muscles decreased femoris [18].

A comparison of the difference in 30STS values after and before treatment between groups using the Independent t-test is presented in Table 5. There were significant differences between groups in the change in 30STS values after 6 weeks of treatment. The effect size using Cohen's d shows a very large value (d> 1). Therefore, adding BFR to low-intensity weight training for 6 weeks significantly impacts changes in the 30STS value of the treatment group compared to the control group.

In this study, the difference in the 30STS value of the treatment group was 3.36±1.216 and 2.00 in the control group ±0.877 in which the comparison of the two groups showed a significantly more significant change in the 30STS value in the treatment group (p-value = 0.002). Gill *et al.* (2021), the minimum detectable change (MDC) value for the 30STS test in a group of patients with knee OA was 0.3-0.4 times. Thus, the results of this study reached the MDC value in both the treatment group and the control group (Gill et al., 2021). The results obtained in this study are in line with a study conducted by Ferraz *et al.* (2018), which compared the effects of low-intensity strengthening exercises (LI-RT) (30% 1-RM), BFR (combined with LI-RT 30% 1-RM), and high-intensity strengthening exercise (HL-RT) (80% 1-RM) in 50-65-years old women with knee OA. There was a significant increase in quadriceps femoris muscle strength ($p<0.05$) in the BFR and HL-RT group compared to the LL-RT group, as measured by a more significant increase in 1-RM value in the BFR and HI-RT group [19]. In addition, the results of this study are also to the conclusions of the Systematic review and meta-analysis conducted by Hughes (2017), which compared the effects of muscle strengthening with the application of BFR, high and low-intensity training [14].

The 30STS test assesses lower extremity muscle strength in the elderly group. Decreased lower extremity muscle strength is associated with decreased ability to sit to stand. Lower extremity muscle strength can reflect or affect the ability to do 30 seconds of sit-to-stand. Jones *et al.* (1999) compared the results of the 30STS test with the 1

RM leg press strength test in groups of elderly men and women and found a moderate-high correlation between the 30STS test and the value of the 1 RM leg press strength test. In the present study, the results of the 30STS examination can describe the strength of lower extremity muscles, especially the hip extensor, knee extensor, and ankle plantar flexor muscle groups [20]. Furthermore, a study by Nakatani *et al.* (2002) assessing the validity of the 30STS test for evaluating lower limb strength showed high reliability, making the 30STS test a good method for evaluating lower limb strength [21-24]. Research on the effect of adding BFR to weight training in patients with knee OA still needs to be completed in Indonesia. To the researchers' knowledge, this study is the first study in Indonesia to assess the LI-RT effect combined with BFR in patients with KOA on lower extremity strength measured by the 30STS test. This study showed a significantly higher in the 30STS score in the group with BFR compared to the control group that only received LI-RT. An increase in lower extremity strength, as assessed by an increase in the 30STS value in patients with knee OA can prevent the disabilities occurrence in patients with knee OA. Similarly, low-intensity weight training with the addition of BFR can provide a more practical approach than low-intensity weight training and is more tolerable than high-intensity weight training with less joint stress, especially in elderly patients, so that weight training with the BFR addition can be an alternative therapy for patients with knee OA who are unable to perform high-intensity weight training. The intervention in this study was for 6 weeks, which the duration of this treatment was relatively shorter compared to previous studies on BFR that mostly on the average training session around 8 to 12 weeks. This can be an advantage of this study, that 6 weeks of LI-RT combined with BFR can increase lower extremity strength as assessed by 30STS. In addition, during the exercise, there were no unwanted side effects, so LI-RT combined with the BFR using our protocol in this study is a safe therapeutic option for patients with KOA. Until now, the prescription of exercises with BFR is still very diverse. Therefore, the results of this study can be useful in enriching scientific references regarding the effect of BFR administration in LI-RT on the lower extremity strength in patients with KOA.

This research has several limitations, including: (1) Subjects were limited to grade 2 and 3 KOA, so the results of this study cannot be generalized to other KOA grades, (2) Researchers did not assess the subject's daily intake, which could affect the increase in muscle mass and strength of the lower extremity, (3) The control group in this study received LI-RT with the same number of repetitions as the BFR group, while the recommended strengthening exercise according to ACSM for KOA is moderate-intensity resistance training.

Conclusion

1. BFR addition in LI-RT of the quadriceps femoris muscle for 6 weeks increases lower extremity strength in patients with KOA.
2. Low-intensity resistance training of the quadriceps femoris muscle for 6 weeks increases lower extremity strength in patients with KOA.
3. BFR addition in LI-RT of the quadriceps femoris muscle for 6 weeks resulted in a significantly greater increase in lower extremity strength compared to the group that only received LI-RT.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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