

# From Anterior Cruciate Ligament Reconstruction to Recovery

Preferences, Predictors and the Potential of  
Blood Flow Restriction Training

Bariş Beytullah Koç





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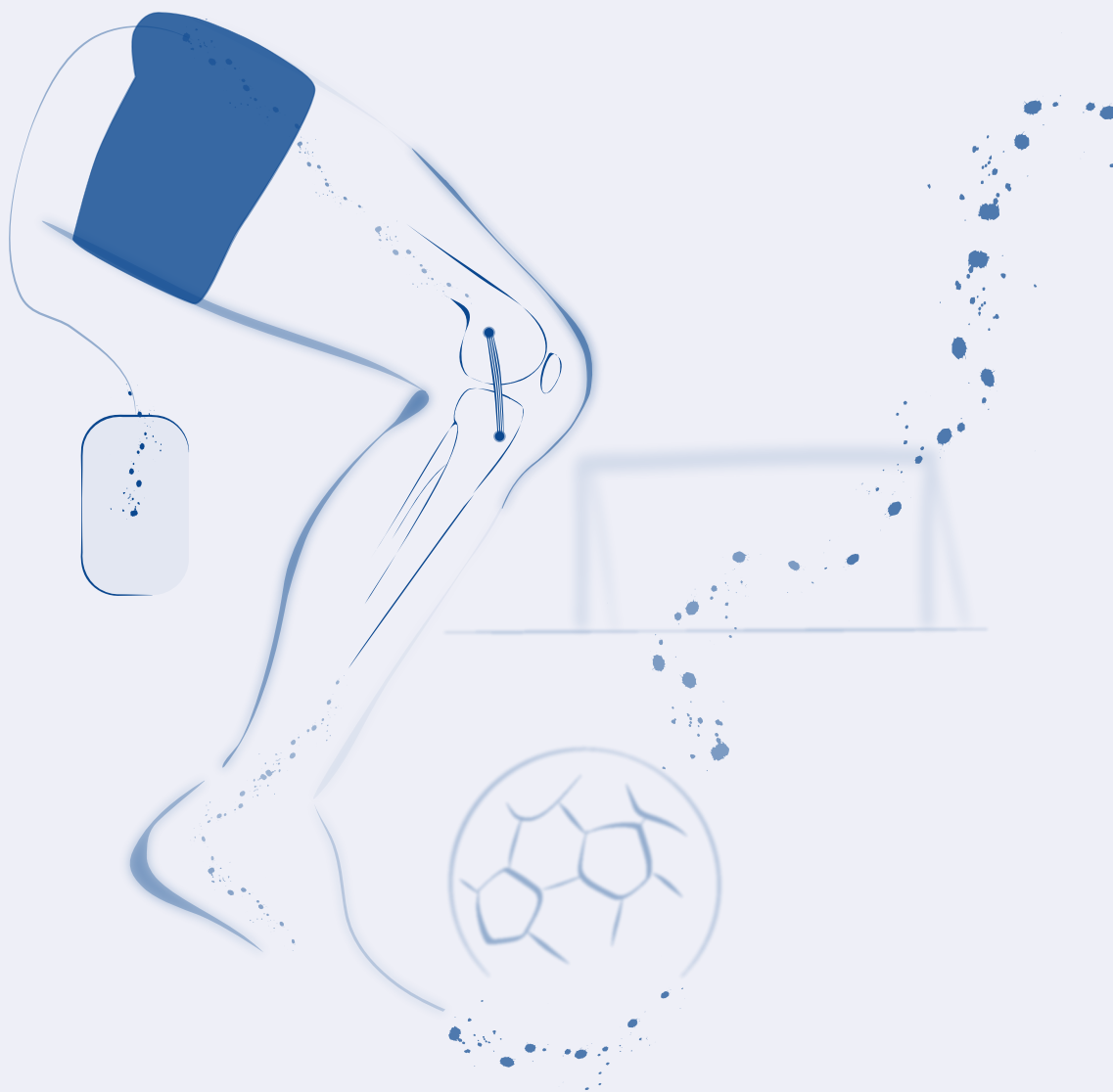
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# Chapter 1

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**General introduction**  
**Thesis outline**

## General introduction

1 As an orthopedic resident, I have always been interested in managing sports injuries of the knee. This interest brought me into contact with physiotherapists and orthopedic surgeons specialized in knee and sports medicine. Through numerous conversations, I gained valuable insights into the outcomes of anterior cruciate ligament (ACL) reconstruction. These conversations highlighted the crucial role of rehabilitation and inspired me to explore the ACL recovery process in greater detail. Additionally, a physiotherapist introduced me to low-load blood flow restriction training (LL-BFRT) in musculoskeletal rehabilitation. However, the role of LL-BFRT following ACL reconstruction was not well-known. This inspired me to pursue this PhD project aiming to optimize ACL reconstruction outcomes and assess the effectiveness of LL-BFRT.

In this general introduction, I will begin by describing the anatomy of the ACL, its epidemiology, and the different techniques used for ACL reconstruction. Following this, I will highlight the current rehabilitation approaches following ACL reconstruction and provide an overview on the application of LL-BFRT. Lastly, I will provide an outline of the thesis.

## ACL anatomy

The ACL is a key stabilizer of the knee joint, extending from the posterior part of the medial wall of the lateral femoral condyle onto the anterior intercondylar area of the tibia (Figure 1) (1,2). The ACL consists of two bundles: the anteromedial bundle, which resists anterior tibial translation, and the posterolateral bundle, which limits tibial internal rotation (1,2). The blood supply to the ACL is primarily provided by the middle genicular artery, with minor contributions from the medial and lateral inferior genicular arteries (1). However, compared to other ligaments such as the medial collateral ligament, the vascularization of the ACL is limited (3). This limited blood supply, combined with avascular zones near the tibial insertion impairs the healing capacity of the ACL (1). The innervation of the ACL is derived from the posterior articular branches of the tibial nerve. Additionally, about 2.5% of the ACL consists of mechanoreceptors, supporting proprioception and neuromuscular control of the knee (1,2).

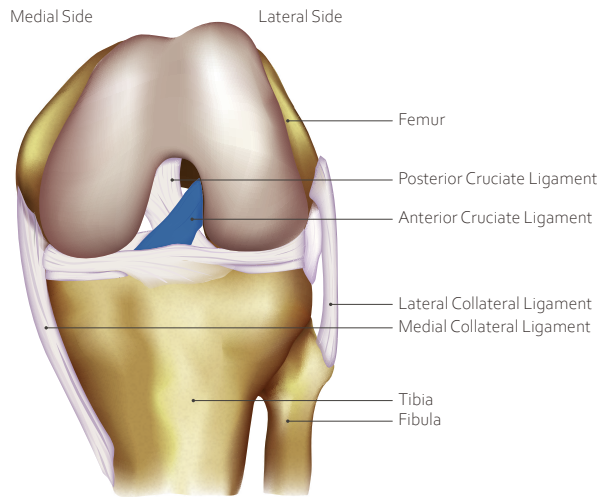


**Figure 1.** An anatomical illustration of the left knee highlighting the anterior cruciate ligament. *Modified with permission from Arliani et al. (2022) 'Three dimensional anatomy of the anterior cruciate ligament: a new approach in anatomical orthopedic studies and a literature review. Illustration by Anastasia Gangaev.*

## Epidemiology

ACL injuries are the most common ligamentous injuries of the knee, with an incidence of 3 to 8 per 10,000 person-years (4,5). In the Netherlands, approximately 10,000 ACL injuries occur annually (6). Females have a threefold increased risk of sustaining an ACL injury compared to males (4,5). This increased risk is due to a combination of anatomical, hormonal, and biomechanical factors (7). The highest risk of ACL injuries in females is between 14 and 18 years of age, while for males it is between 19 and 25 (5). ACL injuries most commonly occur during pivoting sports such as soccer and handball and around 70% of these injuries are caused by a non-contact pivoting movement, including knee valgus and tibial internal rotation (8,9). These injuries are often associated with collateral ligament, meniscal or cartilage injury (10,11). In addition, ACL injuries can result in muscle atrophy and neuromuscular dysfunction (12,13). These factors may contribute to instability of the knee and may compromise quality of life, limit physical activity and increase the risk of early-onset osteoarthritis (13-15).

## ACL reconstruction techniques

The goal in the treatment of ACL injury is to restore knee stability and function while minimizing long-term degenerative changes (14,15). To date, most young athletes with an ACL injury opt for ACL reconstruction, which is the current surgical gold standard. In line with practice in the United States, an increase in primary ACL reconstructions is observed in the Netherlands with more than 8,000 reconstructions performed annually (16,17). The procedure involves the replacement of the ruptured ACL with graft tissue, either harvested from the patient (autograft) or from a donor (allograft) (Figure 2).

The choice of graft tissue is an important consideration in ACL reconstruction, as each graft tissue offers distinct biomechanical properties, healing potentials and risk profiles (18-20). For example, bone-patellar tendon-bone autografts are often preferred for their stability and ability to promote bone-to-bone healing, while hamstring tendon autografts offer less invasive harvesting procedure with potentially lower donor site morbidity (18,19). Allografts, on the other hand, can reduce operative time and avoid donor site morbidity but are associated with higher graft failure rates, especially in young and active individuals (21).

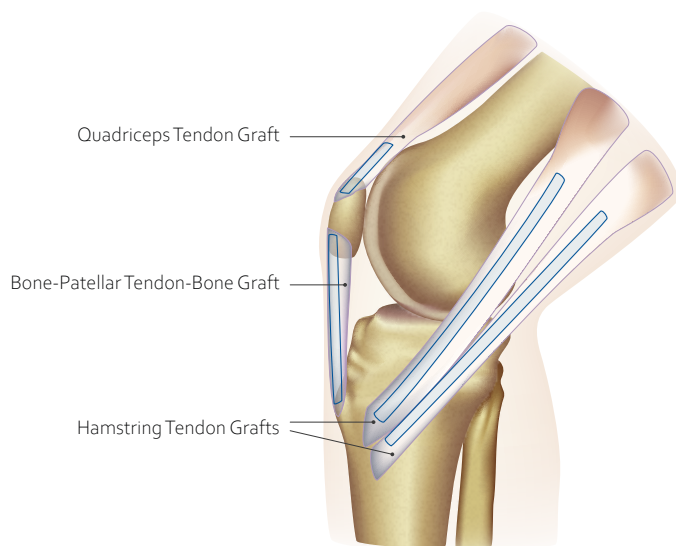


**Figure 2.** A sagittal view of the knee showing the most widely used grafts for ACL reconstruction: bone-patellar tendon-bone, hamstring tendon, and quadriceps tendon. *Modified with permission from ArthurCare patient-education materials (arthurcare.com). Illustration by Anastasia Gangaev.*

Additionally, the surgical technique for femoral and tibial tunnel placement in ACL reconstruction, is a crucial factor in determining the success of the procedure. The position of these tunnels can influence graft tension, knee kinematics, and the risk of graft failure (22).

Over the years, various techniques for femoral and tibial tunnel placement have emerged. These techniques range from traditional approaches, such as the transtibial method, to more anatomically accurate approaches, including the anteromedial and outside-in techniques (Figure 3) (23,24). Anatomic tunnel placement, which aims to closely replicate the native ACL footprint, is increasingly favored as it has been shown to provide better restoration of knee biomechanics compared to non-anatomic techniques (22-24).

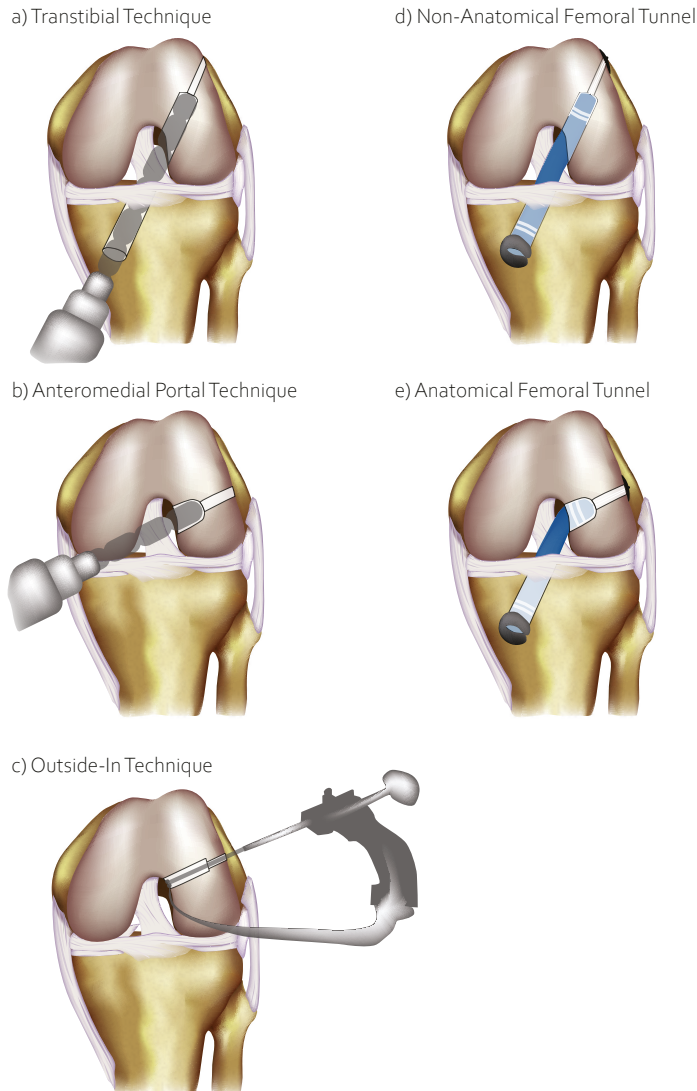


**Figure 3.** A representation of three different femoral tunnel placement techniques (a-c) and the differences between non-anatomic and anatomic graft placement (d-e). Modified with permission from Saliba et al. 'Anterior cruciate ligament reconstruction: antero-medial portal vs trans-tibial femoral tunnel drilling. Illustration by Anastasia Gangaev.

In addition to ACL reconstruction, recent research has increasingly focused on the importance of the anterolateral complex to improve rotational stability. The anterolateral complex includes the superficial and deep iliotibial band (ITB), the capsulo-osseous layer of the ITB and a thickening of the lateral capsule referred to as the anterolateral ligament (25). Lateral extra-articular procedure (LEAP) is a technique that augments ACL reconstruction by reinforcing the anterolateral complex. LEAP can be performed as a lateral extra-articular tenodesis, such as the modified Lemaire technique, which has demonstrated biomechanical equivalence to other LEAPs (Figure 4) (26,27). These procedures have been shown to reduce the rate of re-injury and improve functional outcomes following ACL reconstruction with no significant increased risk of complications such as hematoma and infection (28-30). However, some technical challenges such as tunnel convergence and overconstraint have been recognized (31-33).

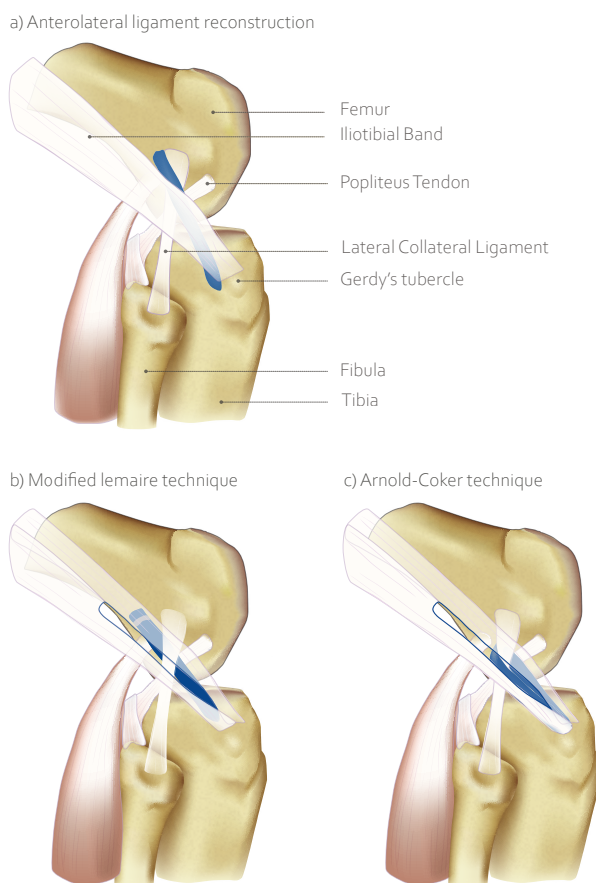


**Figure 4.** An overview of commonly used techniques for LEAP. Modified with permission from Jorge Chahla patient-education materials ([jorgechahlamd.com](http://jorgechahlamd.com)). Illustration by Anastasia Gangaev.

Although ACL reconstruction has been shown to be an effective procedure for ACL injury, around one-third of patients do not return to pre-injury level of sport (34). In addition, re-injury rates are reported to be between 5% and 10% within the first two years, with an increased risk of up to 20% in studies with six- to ten-year follow-up (34-36). These results indicate that surgery is only one component of the recovery process, with rehabilitation playing a crucial role in determining the success of ACL reconstruction.

## Rehabilitation following ACL reconstruction

Rehabilitation following ACL reconstruction has evolved from a time-based to a criteria-based approach (37-40). Postoperative rehabilitation is divided into three phases, each with specific goals to ensure a gradual and safe recovery (Figure 5). However, before discussing postoperative rehabilitation, it is necessary to briefly enlighten pre-operative rehabilitation as pre-operative knee function is associated with postoperative surgical outcome (41,42). Pre-operative extension loss and knee effusion increase the risk of postoperative complications, such as arthrofibrosis (43,44). In addition, pre-operative quadriceps and hamstring strength deficits of more than 20% predict significant strength deficits until two years following ACL reconstruction (45-47). Thus, pre-operative rehabilitation to ensure full knee extension, absent or trace knee swelling and restoration of quadriceps and hamstring muscle strength before surgery is recommended.

Following ACL reconstruction, the early-stage rehabilitation (phase 1) aims to address the effects of surgery and to prepare the patient for the mid-stage rehabilitation (phase 2). The focus is on controlling knee pain and swelling, regaining knee range of motion, initiating muscle activation and restoring normal gait (37,38). Regaining full knee extension is crucial as failure to regain full knee extension within six weeks following ACL reconstruction is a significant predictor of cyclops syndrome and arthrofibrosis (48,49). Additionally, a loss of five degrees of knee extension causes a flexed-knee gait that has been shown to increase joint loading and patellofemoral pain (50-52). As the patient progresses and meets the criteria for the mid-stage rehabilitation (phase 2), the focus of rehabilitation shifts towards regaining muscle strength, improving neuromuscular control and enhancing overall fitness (37-39). However, knee range of motion, swelling control and pain management remain essential throughout each phase of the rehabilitation. One of the main priorities of the mid-stage rehabilitation is regaining quadriceps and hamstring strength (37-39). Quadriceps muscle weakness is associated with abnormal gait, knee pain, lower rates of returning to sports, and a higher risk of re-injury (53-57). Deficits in quadriceps strength of 25%-40% compared to the uninjured leg are common reported six to twelve weeks following ACL reconstruction (56,58-60). These deficits are influenced by factors such as age, gender, pre-operative quadriceps strength, graft choice, knee pain, arthrogenic muscle inhibition

and muscle atrophy post-surgery (42,60-64). Although deficits in hamstring strength are usually less than those in the quadriceps, even small deficits in hamstring strength are associated with increased risk of re-injury (55). A ten-fold increased risk of re-injury is reported for each additional 10% deficit in hamstring to quadriceps strength ratio (55). Before advancing to late-stage rehabilitation (phase 3), the patient must have sufficient muscle strength, neuromuscular control and overall fitness (65,66). The key component of late-stage rehabilitation is on-field sport-specific training with the aim to return to sport and finally return to performance (37,40). On-field rehabilitation progresses from controlled pre-planned exercises running to complex and unpredictable tasks. These aim to replicate the chaotic nature of sports, encouraging the patient to anticipate and react to external stimuli. Previous studies have shown that the addition of external stimuli can induce worse neuromuscular control and increased knee loads. Athletes with neuromuscular deficits during a vertical jump task at the time of return to sport were associated with a three- to eightfold increased risk of ACL re-injury (67). In addition, the completion of sport-specific on-field rehabilitation has been shown to improve safe return to sport (55,65,68). Therefore, optimizing neuromuscular control by sport-specific rehabilitation is crucial for safe return to sport.

For an effective rehabilitation, it is crucial to focus not only on physical recovery but also on the patient's mental and psychological well-being. This is important to determine a successful return to sport, as a systematic review reported that 65% of patients refrained from returning to sport due to psychological factors, with fear for re-injury as the most common reason (69).

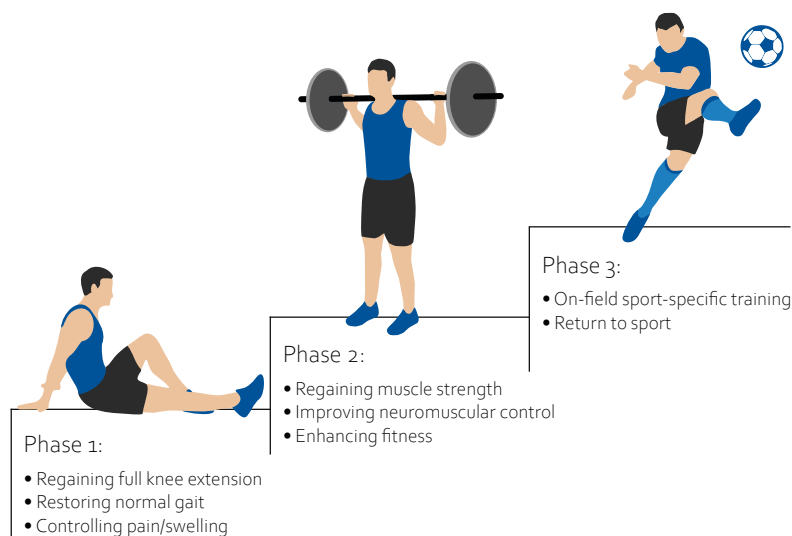


**Figure 5.** An overview of rehabilitation phases following ACL reconstruction. *Illustration by Anastasia Gangaev.*

## Low-load blood flow restriction training

A major challenge in ACL rehabilitation is regaining muscle strength while avoiding excessive stress on the knee joint. Traditional heavy-load resistance training (HLRT), using external loads of more than 60% of the one-repetition maximum (1RM), is the current gold standard to promote muscle strength (Figure 6) (70). However, despite the recognized benefits of HLRT for muscle strength improvements, there are concerns regarding its application during ACL rehabilitation (71-73). HLRT in the early phases of ACL rehabilitation may place excessive stress on the knee joint. This challenge has led to the exploration of alternative training methods that can safely promote muscle strength during the early phases of ACL rehabilitation. One such method that has gained considerable attention in recent years is low-load resistance training (LLRT), using external loads between 20 and 40% of 1RM, in combination with blood flow restriction (BFR) (74,75).

BFR involves the application of a pneumatic cuff on the proximal part of the limb to restrict arterial blood inflow while occluding venous outflow (Figure 6) (74,75). The addition of BFR to LLRT creates a hypoxic environment and induces metabolic stress much earlier than in standard LLRT (75-77). This results in the early recruitment of fast-twitch muscle fibers and triggering anabolic signaling pathways (75-77). This accelerated metabolic environment enables significant muscle mass and strength adaptations with lower external loads than would be required without BFR (75).

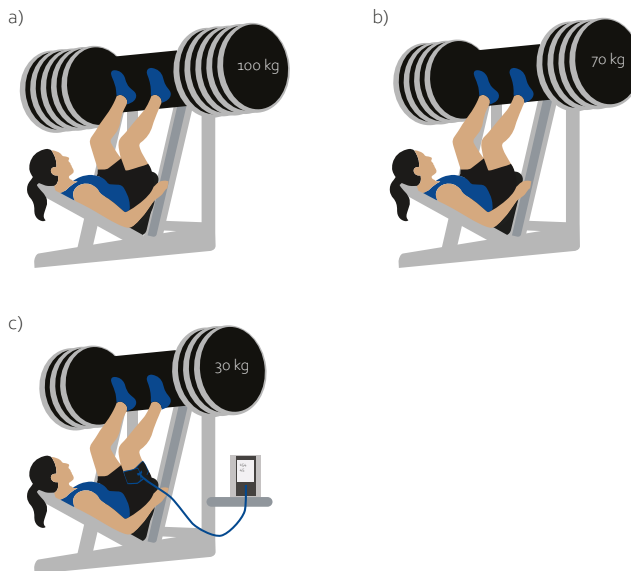


**Figure 6.** A comparison of external-loads based on one-repetition maximum of 100kg: (a) 100% of one-repetition maximum, (b) 70% of one-repetition maximum, and (c) 30% of one-repetition maximum combined with blood flow restriction. *Illustration by Anastasia Gangaev.*

BFR training was developed in the 1960s by Yashiaki Sato, a Japanese innovator (Figure 7). Sato's innovation, originally termed "Kaatsu training", was inspired by his experience of muscle fatigue caused by restricted blood flow during a traditional Buddhist ceremony. He began experimenting with compressive bands to control blood flow during exercise. This eventually led to the development of BFR training, which stimulates muscle growth while minimizing mechanical stress on joints and tendons. Over the years, this technique evolved from simple elastic bands used by Sato to modern pneumatic cuffs that allow for more precise control of blood flow. These advancements have improved the safety and effectiveness of BFR training. As a result, BFR training is becoming increasingly popular in elite sports and rehabilitation.



**Figure 7.** An illustration of Yashiaki Sato's original non-pneumatic cuffs to today's advanced pneumatic and computerized cuffs. *Reproduced from KAATSU patient-education materials (kaatsu.com).*

## Thesis outline

Anterior cruciate ligament (ACL) reconstruction is one of the most performed orthopedic surgeries. The success of ACL reconstruction is influenced by various factors such as surgical technique, patient characteristics and rehabilitation. Although, blood flow restriction (BFR) training is an increasingly popular method in elite sports and rehabilitation, its role following ACL reconstruction is unknown. The purpose of this thesis is to gain insight on surgical techniques of ACL reconstruction in the Netherlands, evaluate predictors for successful outcome and investigate the role of low-load BFR training in ACL rehabilitation.

## Part I ACL reconstruction in the Netherlands

In **Chapter 2**, the current state of ACL reconstruction in the Netherlands is evaluated by performing a web-based survey among members of the Dutch Association of Arthroscopy (NVA). The survey is used to gain insight on preferences regarding technique for femoral tunnel placement, graft selection and defining criteria to evaluate readiness to return to sport.

## Part II Predictors of ACL reconstruction outcome

The outcome of ACL reconstruction is commonly reported as return to pre-injury level of sport, patient reported knee function and quality of life. However, studies evaluating patient satisfaction following ACL reconstruction are limited. Furthermore, predictors of patient satisfaction with the outcome of ACL reconstruction are not well-known. In **Chapter 3**, we present a retrospective study evaluating predictors of patient satisfaction following ACL reconstruction. In addition, we investigated whether patient satisfaction is associated with pre-injury level of sport, patient reported knee function and quality of life.

## Part III Low-load BFR training post-ACL surgery

In **Chapter 4**, we reviewed the literature to evaluate the role of low-load BFR training following ACL reconstruction. The goal was to investigate BFR training protocols and evaluate the effects on quadriceps strength, quadriceps mass, knee joint pain and ACL graft laxity compared to training without BFR. Following this review, **Chapter 5** presents a randomized controlled trial comparing low-load BFR training and heavy-load resistance (HLR) training in the early postoperative phase following ACL reconstruction on muscle strength, knee joint pain, knee joint effusion and range of motion. In **Chapter 6**, we present a qualitative analysis on patient experiences with low-load BFR and HLR training. Finally, in **Chapter 7**, the findings of the previous studies are discussed. In addition, implications and recommendations for future research are presented.

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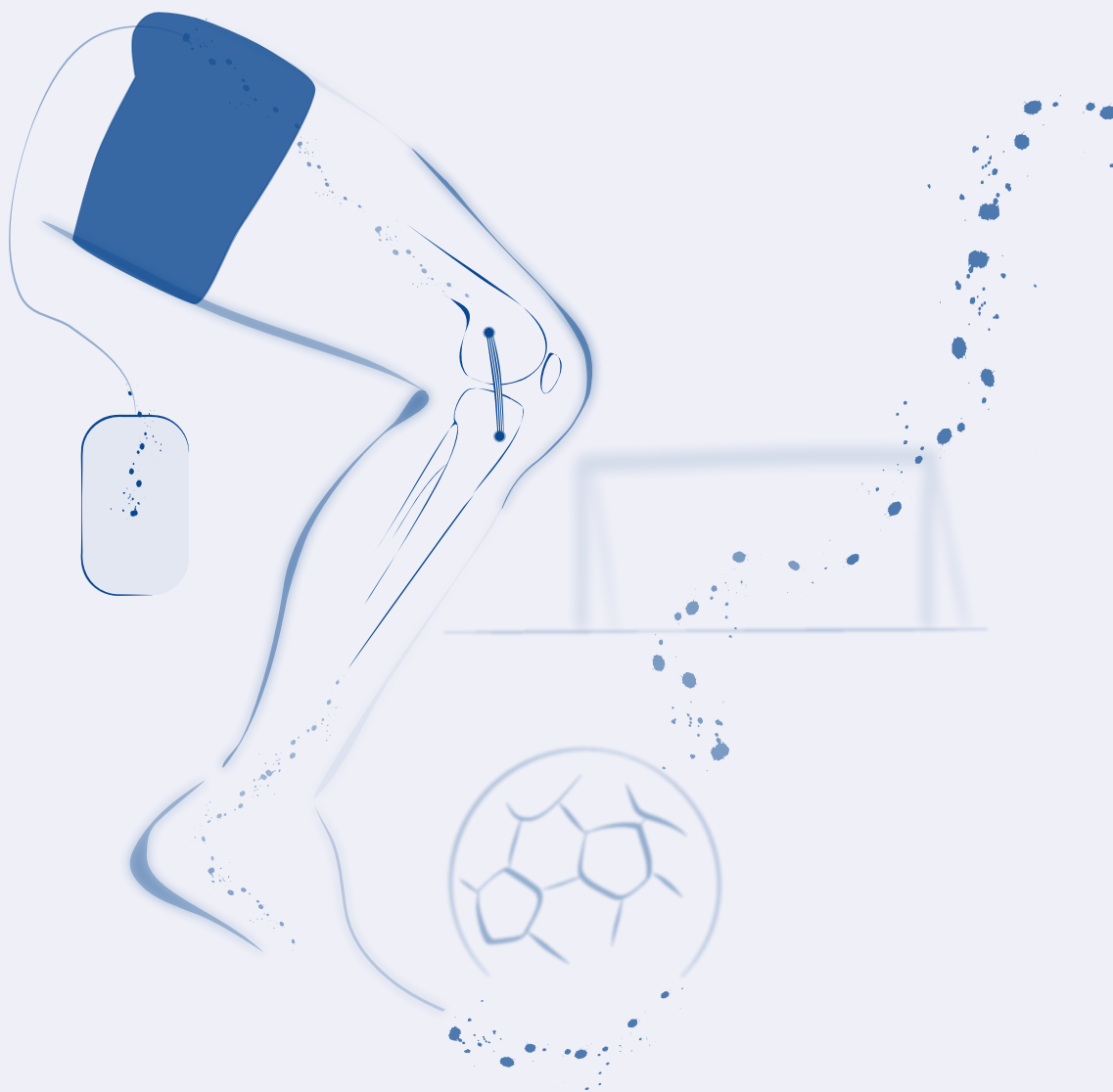




# Part I

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ACL reconstruction in the Netherlands



# Chapter 2

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## **Preferences in anterior cruciate ligament reconstruction and return to sport: a survey among surgeons in the Netherlands**

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*J Clin Orthop Trauma, 2021;12:183-186*

## Abstract

**Objective:** The purpose of this study was to investigate the preferences of surgeons on technique for femoral tunnel placement, graft selection and criteria for return to sport in the Netherlands.

**Methods:** A web-based survey among the Dutch Association of Arthroscopy was conducted.

**Results:** A total of 125 members (24.0%) were included in the analysis. A total of 87.2% (n = 109) used hamstring autografts for primary ACL reconstruction followed by patellar tendon autograft (n = 11, 8.8%) and quadriceps tendon autograft (n = 5, 4.0%). The anteromedial technique was favored by 50.4% (n = 63), whereas 11.2% (n = 14) of the participants favored the transtibial technique. Return to sport after 9 months of primary ACL reconstruction was allowed by 75.2% (n = 94) of the participants. Regarding criteria to evaluate readiness to return to sport, the surgeons stated postoperative period (n = 107, 85.6%) and functional performance tests (n = 96, 76.8%) as important.

**Conclusion:** The majority of the participants of the Dutch Association of Arthroscopy favored the hamstring autografts for primary anterior cruciate ligament reconstruction. Furthermore, most participants stated postoperative time and functional performance tests as important criteria to evaluate readiness to return to sport. This is the first survey demonstrating a high preference of surgeons to use functional performance tests in the decision-making of readiness to return to sport.

## Introduction

The anterior cruciate ligament (ACL) plays an important role in the stability of the knee (1). Injury to the ACL is common in pivoting sports and leads to instability and dissatisfaction (2,3). An ACL reconstruction is recommended in patients who intend to return to high-level sports (4). In line with the United States, an increase in primary ACL reconstructions is observed in the Netherlands with more than 8.000 reconstructions performed annually (5,6). Despite the increasing incidence of primary ACL reconstructions, controversy remains regarding the optimal technique for femoral tunnel placement, selecting the optimal graft and defining criteria to evaluate readiness to return to sport (7-9). A web-based survey was developed to investigate the preferences of a Dutch community of surgeons regarding technique for femoral tunnel placement, graft selection and criteria to evaluate readiness to return to sport.

## Methods

Between October and November 2018, a survey on preferences regarding technique for femoral tunnel placement, graft selection and defining criteria to evaluate readiness to return to sport was performed among members of the Dutch Association of Arthroscopy (NVA). An online survey tool was used to collect anonymous data from the members of the NVA. The survey consisted of 6 questions including: surgeon's experience, femoral tunnel placement, graft selection and defining criteria for return to sport. The results of each question were expressed as the proportion of respondents (%).

## Results

In total 176 (33.8%) of the 520 members completed the survey. Fifty-one members reported not performing an ACL reconstruction and therefore data of 125 (24.0%) members were used in this survey.

### Surgeon's experience

Regarding the surgical experience in ACL reconstruction, 68.0% (n = 85) of the participants reported performing more than 25 procedures per year (Figure 1). Furthermore, 47.2% (n = 59) of the participants have more than 10 years of experience (Figure 2).

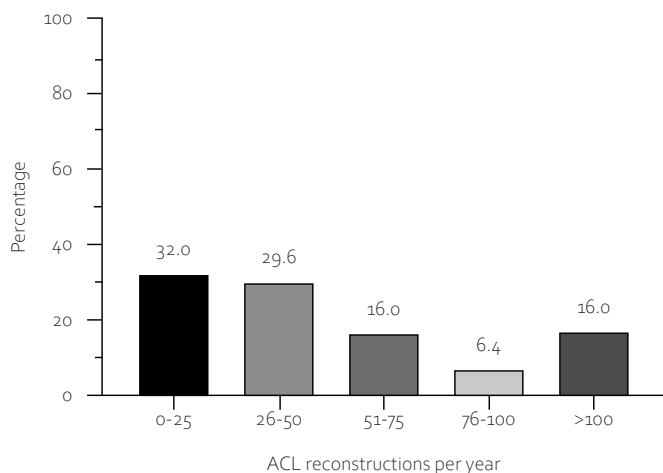


**Figure 1.** Frequency distribution of participants performing anterior cruciate ligament reconstructions per year.

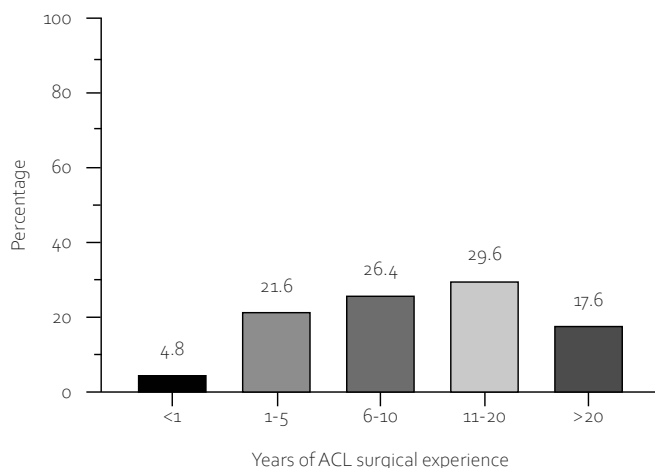


**Figure 2.** Years of anterior cruciate ligament surgical experience among the participants.

## Technique for femoral tunnel placement

The anteromedial technique was favored by 50.4% ( $n = 63$ ), whereas 11.2% ( $n = 14$ ) of the participants favored the transtibial technique. The outside-in technique was used by 38.4% ( $n = 48$ ) of the participants.

## Graft selection

A total of 87.2% ( $n = 109$ ) used hamstring autografts for primary ACL reconstruction followed by patellar tendon autograft ( $n = 11$ , 8.8%) and quadriceps tendon autograft ( $n = 5$ , 4.0%). None of the participants used allografts.

## Criteria for return to sport

Most of the participants ( $n = 94$ , 75.2%) allowed return to sport after 9 months of primary ACL reconstruction (Figure 3). None of the participants allowed return to sport before 6 months of ACL reconstruction. Regarding criteria to evaluate readiness to return to sport, the surgeons stated postoperative period ( $n = 107$ , 86.3%) and functional performance tests ( $n = 96$ , 76.8%) as important. Clinical examination and patient reported outcome measurement were stated as important criteria for return to sport by 56.8% ( $n = 71$ ) and 43.2% ( $n = 54$ ) of the participants, respectively.

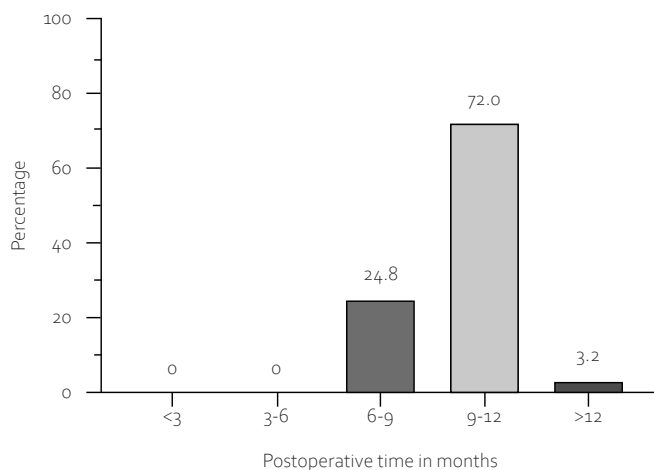


**Figure 3.** Trends of return to sport after primary anterior cruciate ligament reconstruction.

## Discussion

The majority of the participants of the Dutch Association of Arthroscopy (NVA) favored hamstring autografts for primary anterior cruciate ligament (ACL) reconstruction. In addition, most participants stated postoperative time and functional performance tests as important criteria to evaluate readiness to return to sport. This is the first survey demonstrating a high preference of surgeons to use functional performance tests in the decision-making of readiness to return to sport.

The majority (50.4%) of the participants of the NVA favored the anteromedial technique, whereas 11.4% favored the transtibial technique. The preference for the anteromedial technique is in line with other surveys, ranging from 57 to 89% (10-16). The fact that the anteromedial technique is favored above the transtibial technique could be explained as the anteromedial technique provides a more accurate anatomic placement of the femoral tunnel (17). The current study showed a higher percentage of participants favoring the

outside-in technique compared to the literature: 38.4% and 15.0%, respectively (10,11). The outside-in technique is less-technical demanding than the anteromedial technique while ensuring an accurate anatomic placement of the femoral tunnel (18). However, this technique needs an additional lateral incision and no long-term follow-up studies exist (18).

Most participants (87.2%) preferred hamstring autografts for primary ACL reconstruction followed by patellar tendon autograft (8.8%). This was in line with other national and international societies (45–95%) preferred hamstring autografts and 2–41% preferred patellar tendon autografts (10-15,19-23). However, in competitive athletes a higher preference for patellar tendon autografts was described in recent studies, ranging from 45 to 86% (16,20,24,25). A systematic review supposed a shorter maturation time of the patellar tendon autograft compared to hamstring autografts (26). In addition, higher failure rates with hamstring tendon autografts compared with patellar tendon autografts were observed in a recent randomized controlled trial (27). These findings could contribute to a higher preference of patellar tendon autografts in primary ACL reconstruction in the future.

In the current survey, postoperative time was stated as the most important criterion to evaluate readiness to return to sport. Return to sport 9 months after primary ACL reconstruction was allowed by 75% of the participants. This was in line with German arthroscopic surgeons allowing return to sport after 8 months in 63% of cases (23). However, an earlier return to sport was allowed by other national and international societies. The majority of the members (92%) of the Croatian Orthopaedic and Traumatology Association allowed return to sport before 9 months (13). The members of the Canadian Orthopaedic Association stated to allow return to sport before 9 months in 60% of the cases (19). A similar early return to sport before 9 months (65%) was observed by the members of the American Orthopaedic Society of Sports Medicine and the Arthroscopy Association of North America (15). The Major League Soccer Team Physicians and NFL and NCAA Football Team Physicians allowed return to sport before 9 months in 82% and 68% of the cases, respectively (16,25). The SIGASCOT members allowed return to non-contact and contact sports before 8 months in 92% and 72% of the cases, respectively (20). The Brazilian orthopedic surgeons and Turkish ACL surgeons allowed return to sport 6 months after ACL reconstruction in 80% of the cases (21,22). The reason for an earlier return to sport compared to our study is unknown, as femoral tunnel placement and graft selection were comparable.

The importance of postoperative time has been illustrated in animal studies (28). Animal studies demonstrated that the remodeling process consisted of three phases: a necrosis phase, a proliferation phase and a ligamentization phase (28). The remodeling process towards an intact ACL takes around 6–12 months (28). Furthermore, a recent study

observed a decreased risk of re-injury by 153% when return to sport was delayed from 6 to 9 months after ACL reconstruction (29).

In addition to postoperative time, 78% of the participants of the NVA stated functional performance tests as important criterion to evaluate readiness to return to sport. Functional performance tests were used in the decision-making of return to sport by around 40% of German arthroscopic surgeons and members of the Italian Society of Knee, Arthroscopy, Sport, Cartilage and Orthopaedic Technologies (SIGASCOT) (20,23). The importance of functional tests have been described in literature (30,31). Kyrisitis et al. demonstrated that athletes who do not meet functional performance criteria had increased risk of graft rupture (30). Furthermore Hildebrandt et al., showed that functional performance tests could determine readiness for return to sport (31). However, different functional performance tests have been described in literature (32). Furthermore, there is no consensus on which functional performance tests to use in the decision-making of return to sport. The optimal functional performance tests should be consistent, valid, low in price, easy to use and easy to interpret.

This study has several limitations. First of all, the response rate was 33.8%. However, the response rate was comparable with other national and international studies (16–50%) (13,19,20). This response rate could be explained by non-active members and members not involved in knee surgery. Furthermore, with 125 participants in the current study, we have a higher number of respondents compared to surveys presenting results of <50 participants (21,25). Secondly, the current survey highlights the preferences among surgeons in the Netherlands rather than a guideline for clinical practice.

## Conclusion

The majority of the participants of the Dutch Association of Arthroscopy favored the hamstring autografts for primary anterior cruciate ligament reconstruction. Furthermore, most members stated postoperative time and functional performance tests as important criteria to evaluate readiness to return to sport. This is the first survey highlighting the preference of surgeons to use functional performance tests in the decision-making of readiness to return to sport.

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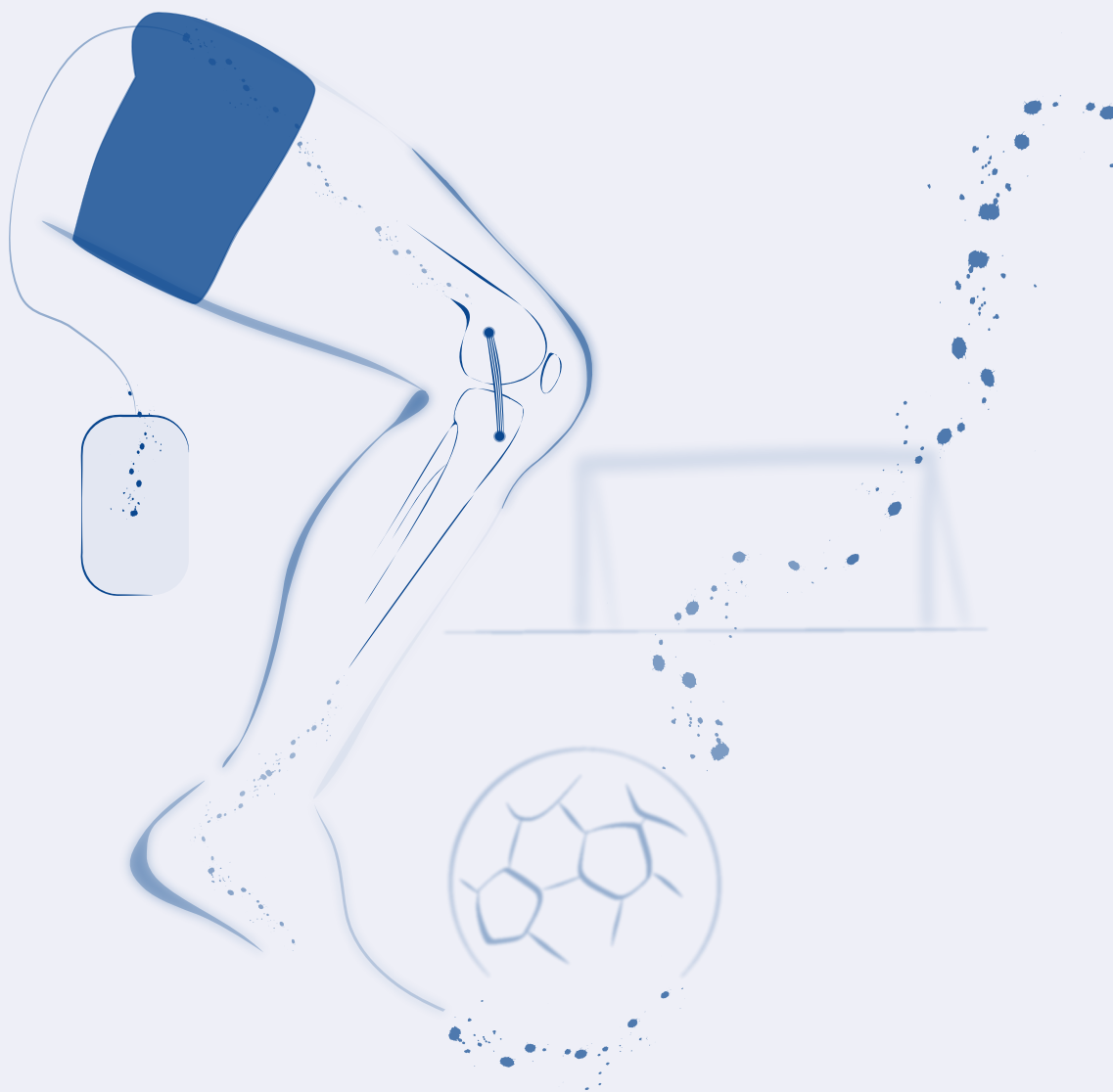
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# Part II

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Predictors of ACL reconstruction outcome



# Chapter 3

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## **Predictors of patient satisfaction after primary hamstring anterior cruciate ligament reconstruction**

B.B. Koc, A.E. Ronden, T.P.M.J. Vluggen, M.G.M. Schotanus, E.J.P. Jansen

*Knee, 2022;34:246-251*

## Abstract

**Background:** Predictors of patient satisfaction (PS) after anterior cruciate ligament (ACL) reconstruction are not well known. This study investigated predictors of PS and whether PS was associated with pre-injury level of sport participation, patient reported knee function and quality of life after ACL reconstruction.

**Methods:** Patients who underwent primary hamstring ACL reconstruction between January 2015 and December 2017 were retrospectively evaluated. An online survey was used to evaluate PS (yes = satisfied, no = unsatisfied), duration of supervised postoperative rehabilitation, timing of return to pre-injury level of sport, pre-injury level of sport participation, patient reported knee function and quality of life. Preoperative, operative and postoperative variables were collected from the medical records.

**Results:** A total of 183 patients completed the survey at a median of 3.6 (1.5) years after ACL surgery. At final follow-up, 82% of patients were satisfied with the outcome. Preoperative (e.g. age) and operative (e.g. meniscal tear) variables were not predictors of PS ( $p > 0.05$ ). Duration of supervised postoperative rehabilitation, timing of return to pre-injury level of sport and postoperative ACL injury were predictors of PS ( $p = 0.018$ ,  $p = 0.016$  and  $p < 0.001$ , respectively). Pre-injury level of sport participation was significantly higher in satisfied compared to unsatisfied patients: 44.7% ( $n = 67$ ) versus 18.2% ( $n = 6$ ) ( $p = 0.005$ ). In addition, satisfied patients reported significantly higher patient reported knee function and quality of life compared to unsatisfied patients ( $p < 0.001$ ).

**Conclusion:** This study provided data on predictors of PS after primary ACL reconstruction. Furthermore, PS was associated with pre-injury level of sport participation, patient reported knee function and quality of life.

## Introduction

In line with the United States, an increase in primary anterior cruciate ligament (ACL) reconstructions is observed in European countries (1,2). As the annual cost of ACL reconstructions is estimated to be \$2 billion in the United States alone, it is important to evaluate the outcome of ACL reconstruction (3).

The outcome of ACL reconstruction is commonly reported as return to pre-injury level of sport, patient reported knee function and quality of life (4-6). However, studies evaluating patient satisfaction (PS) after ACL reconstruction are limited and have declined over the past several years (7). Nevertheless, PS is important as it evaluates whether the outcome is valuable to the patient (8). Studies demonstrated that patient expectations and postoperative knee symptoms predict PS after ACL reconstruction (9,10). Yet, predictors of PS with the outcome of ACL reconstruction are not well known. Furthermore, the diversity of patients' preoperative, operative and postoperative variables makes prediction of PS after ACL reconstruction difficult. Therefore, the main aim of the present study was to identify preoperative, operative and postoperative predictors of PS after primary hamstring ACL reconstruction. The second purpose was to investigate whether PS was associated with pre-injury level of sport participation, patient reported knee function and quality of life. Firstly, we hypothesized that preoperative, operative and postoperative variables predict PS after ACL reconstruction. Secondly, we hypothesized that PS is associated with pre-injury level of sport participation, patient reported knee function and quality of life.

## Materials and Methods

This retrospective study was approved by the medical ethical committee of Zuyderland Medical Center and all patients provided informed consent before enrollment (METCZ20180149).

Patients who underwent primary hamstring ACL reconstruction performed by one experienced orthopedic surgeon between January 2015 and December 2017 were included. Exclusion criteria were posterolateral corner injury, posterior cruciate ligament injury or no participation in level I or II sports prior to ACL injury. Level of sport participation was based on the Cincinnati Sports Activity Scale (11). Patients meeting the selection criteria were contacted to complete an online survey.

All ACL reconstructions were performed in an outpatient setting at Zuyderland Medical Center, Sittard-Geleen, the Netherlands. All patients underwent a single-bundle triple-stranded ACL reconstruction using an autologous semitendinosus and gracilis graft. The anteromedial technique was used for femoral tunnel placement. An endobutton (ToggleLoc™, Biomet, Indiana, United States) was used for femoral graft fixation and a

bioabsorbable interference screw (ComposiTCP™, Biomet, Indiana, United States) for tibial graft fixation. The postoperative rehabilitation was guided by local physical therapists and did not follow a standardized rehabilitation protocol. Furthermore, no standardized return to sport criteria were used.

All preoperative and operative variables were collected from the electronic medical records. The preoperative variables were age, gender, body mass index (BMI), pre-injury activity level, mechanism of injury, grade 2-3 medial collateral ligament injury, previous ipsilateral knee surgery and previous contralateral ACL reconstruction. The grade of medial collateral ligament injury was based on the Fetto and Marshall classification (12). The operative variables were graft size, meniscal tear, meniscal intervention, grade 3-4 cartilage injury and cartilage intervention. The grade of cartilage injury was based on the International Cartilage Repair Society classification (13). Furthermore, postoperative ACL injury was collected from the electronic medical records. ACL injury was defined as ACL re-injury or contralateral ACL injury. An online survey was used to collect data on PS, duration of supervised postoperative rehabilitation (<9 months or ≥9 months), timing of return to pre-injury level of sport (<9 months or ≥9 months), pre-injury level of sport participation (yes or no), patient reported knee function and quality of life. PS was evaluated by asking if the patient was satisfied with the outcome after ACL reconstruction (yes=satisfied, no=unsatisfied). In addition, PS was assessed with the use of a numerical rating scale (0 to 10, 10 being very satisfied). The patient reported knee function included the International Knee Documentation Committee (IKDC) (14). Quality of life was evaluated with the EuroQol-5 Domains (EQ-5D) and the EuroQoL-Visual Analogue Scale (EQ-VAS) (15,16).

## Statistics

SPSS Version 24.0 (IBM Corp, Chicago, IL, USA) was used for statistical analysis. Comparisons of categorical variables were made using chi-square tests and were presented as numbers and percentages. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were tested with parametric t-test and were reported with a mean and standard deviation (SD). Not-normally distributed data were reported by median and interquartile range (IQR). Nonparametric univariate analysis was performed with the Mann-Whitney U test for comparison of two groups and with the Kruskal-Wallis analysis of variance for comparison of multiple groups. The level of statistical significance was set at  $p < 0.05$ .

## Results

### Patient satisfaction

Out of 251 patients contacted, 183 patients completed the online survey (72.3%) at a median of 3.6 (1.5) years after ACL surgery. At final follow-up, 82% of patients were satisfied with the outcome after ACL reconstruction. The median PS score was 8.0 (2.0).

### Predictors of patient satisfaction

#### Preoperative variables

Table 1 shows the preoperative variables of PS. No statistically significant differences in preoperative variables were found between satisfied and unsatisfied patients.

**Table 1.** Preoperative variables of patient satisfaction.

| Variables                                          | Satisfied<br>(n=150) | Unsatisfied<br>(n=33) | p-value |
|----------------------------------------------------|----------------------|-----------------------|---------|
| Age in years, median (IQR)                         | 26.0 (8.0)           | 26.0 (8.5)            | 0.850   |
| Male, n (%)                                        | 96 (64.0)            | 22 (66.7)             | 0.772   |
| BMI in kg/m <sup>2</sup> , median (IQR)            | 23.0 (3.0)           | 24.0 (4.0)            | 0.443   |
| Pre-injury activity level I, n (%)                 | 124 (82.7)           | 29 (87.9)             | 0.464   |
|                                                    | 26 (17.3)            | 4 (12.1)              |         |
| Non-contact mechanism of injury, n (%)             | 133 (88.7)           | 29 (87.9)             | 1.000   |
| Grade 2-3 medial collateral ligament injury, n (%) | 16 (10.7)            | 2 (6.1)               | 0.536   |
| Previous ipsilateral knee surgery, n (%)           | 22 (14.7)            | 9 (27.3)              | 0.080   |
| Previous contralateral ACL reconstruction, n (%)   | 7 (4.7)              | 3 (9.1)               | 0.390   |

ACL, anterior cruciate ligament; BMI, body mass index.

#### Operative variables

Table 2 gives an overview of the operative variables of PS. No statistically significant differences in operative variables were observed between satisfied and unsatisfied patients.

**Table 2.** Operative variables of patient satisfaction.

| Variables                         | Satisfied<br>(n=150) | Unsatisfied<br>(n=33) | p-value |
|-----------------------------------|----------------------|-----------------------|---------|
| Graft size in mm, median (IQR)    | 9.0 (1.0)            | 9.0 (0.5)             | 0.909   |
| Meniscal tear, n (%)              | 57 (38.0)            | 16 (48.5)             | 0.265   |
| Meniscal intervention, n (%)      | 48 (32.0)            | 12 (36.4)             | 0.629   |
| Grade 2-3 cartilage injury, n (%) | 18 (12.0)            | 3 (9.1)               | 0.771   |
| Cartilage intervention, n (%)     | 3 (2.0)              | 2 (6.1)               | 0.221   |

### Postoperative variables

Table 3 shows the postoperative variables of PS. Significantly more satisfied patients followed a supervised rehabilitation  $\geq 9$  months compared to unsatisfied patients: 72.7% (n=109) versus 51.5% (n=17) ( $p=0.018$ ). Significantly less satisfied patients returned to pre-injury level of sport  $< 9$  months compared to unsatisfied patients: 15.3% (n=23) versus 33.3% (n=11) ( $p=0.016$ ). Postoperative ACL injury was less frequently observed in satisfied compared to unsatisfied patients: 4.0% (n=6) versus 57.6% (n=19) ( $p<0.001$ ). Duration of follow-up was not significantly different between satisfied and unsatisfied patients.

**Table 3.** Postoperative variables of patient satisfaction.

| Variables                                               | Satisfied<br>(n=150) | Unsatisfied<br>(n=33) | p-value   |
|---------------------------------------------------------|----------------------|-----------------------|-----------|
| Follow-up in years, median (IQR)                        | 3.7 (1.5)            | 3.5 (1.5)             | 0.961     |
| Rehabilitation $< 9$ months, n (%)                      | 41 (27.3)            | 16 (48.5)             | 0.018     |
| Return to pre-injury level of sport $< 9$ months, n (%) | 23 (15.3)            | 11 (33.3)             | 0.016     |
| Postoperative ACL injury, n (%)                         | 6 (4.0)              | 19 (57.6)             | $< 0.001$ |

ACL, anterior cruciate ligament.

### Association between patient satisfaction and pre-injury level of sport participation, patient reported knee function and quality of life

Table 4 shows an overview of pre-injury level of sport participation, patient reported knee function and quality of life between satisfied and unsatisfied patients. Satisfied patients more likely participated in pre-injury level of sport compared to unsatisfied patients: 44.7% (n=67) versus 18.2% (n=6) ( $p=0.005$ ). The median patient reported knee function was significantly higher in satisfied compared to unsatisfied patients: 89.7 (12.9) versus 69.0 (28.8) ( $p<0.001$ ). In addition, satisfied patients reported significantly higher EQ-5D and EQ-VAS than unsatisfied patients ( $p<0.001$ ).

**Table 4.** Patient satisfaction and pre-injury level of sport participation, patient reported knee function and quality of life at final follow-up.

|                                                | Satisfied<br>(n=150) | Unsatisfied<br>(n=33) | p-value   |
|------------------------------------------------|----------------------|-----------------------|-----------|
| Pre-injury level of sport participation, n (%) | 67 (44.7)            | 6 (18.2)              | 0.005     |
| IKDC, median (IQR)                             | 89.7 (12.9)          | 69.0 (28.8)           | $< 0.001$ |
| EQ-5D, median (IQR)                            | 100.0 (13.3)         | 83.3 (20.5)           | $< 0.001$ |
| EQ-VAS, median (IQR)                           | 90.0 (13.5)          | 80.0 (10.0)           | $< 0.001$ |

EQ-5D, EuroQol-5 Domains; EQ-VAS, EuroQol-Visual Analogue Scale; IKDC, International Knee Documentation Committee.

## Discussion

The most important finding of the present study was that duration of supervised postoperative rehabilitation, timing of return to pre-injury level of sport and postoperative anterior cruciate ligament (ACL) injury were predictors of patient satisfaction (PS) after primary hamstring ACL reconstruction. In addition, PS was associated with pre-injury level of sport participation, patient reported knee function and quality of life.

In the present study, at a median of 3.6 years after ACL reconstruction 82% of patients were satisfied. Furthermore, the median PS score was 8.0. In the current literature, satisfaction ranged from 67 to 100% at an average of 3 years after primary ACL reconstruction (6,10,17,18). The PS score ranged from 4 to 9 (10,19). Differences in results of PS may be due to variations in measurement methods and definitions of PS. Studies measured PS with the use of binary, ordinary or numerical scales (6,10,19). Furthermore, studies defined PS as satisfaction with cosmesis, knee function, activity level or outcome after ACL reconstruction (6,10,17-19).

The present single-center, single-surgeon retrospective study aimed to identify predictors of PS with the outcome after primary hamstring ACL reconstruction. Preoperative variables such as age, gender, pre-injury activity level and grade 2-3 medial collateral ligament injury were not predictors of PS after ACL reconstruction. These findings are in line with previous studies on PS after ACL surgery (6,10). In addition to the literature, the present study demonstrated that body mass index (BMI) and mechanism of injury were not predictors of PS. These results add value to studies reporting that BMI and mechanism of injury have no effect on return to sport and patient reported knee function after ACL reconstruction (5,20,21). The present study furthermore observed that previous ipsilateral knee surgery and previous contralateral ACL reconstruction were not predictors of PS. In the literature, patients with previous knee surgery were associated with lower patient reported knee function after ACL surgery compared to patients without previous knee surgery (22,23). As the number of patients with previous knee surgery were relatively low in the present study, the sample size might have been too small to detect an effect on PS.

In regard to operative variables, the present study observed no predictors of PS with the outcome after ACL surgery. The median graft size was comparable between satisfied and unsatisfied patients. This finding adds value to the current literature showing no association between graft size and patient reported knee function after ACL reconstruction (24). In addition, recent registry studies reported no association between graft size and risk for ACL revision surgery (25,26). The present study furthermore found that concomitant meniscal tear, meniscal intervention, cartilage injury and cartilage intervention were not predictors of PS. One previous study also found no association between cartilage injury and PS after primary ACL reconstruction (10). However, less satisfaction was observed in

patients with lateral meniscal tear compared to patients without lateral meniscal tear (10). In the literature, concomitant meniscal tear or cartilage injury have shown to predict worse patient reported knee function after ACL reconstruction compared to isolated ACL injury (27,28). Yet, as there is only one previous study evaluating the effect of concomitant injury on PS after primary ACL reconstruction, additional research on this topic is needed (10).

Regarding postoperative variables, the present study observed that duration of supervised rehabilitation, timing of return to pre-injury level of sport and ACL injury were predictors of PS. Therefore, these results support the influence of supervised rehabilitation, timing of return to sport and postoperative ACL injury on the outcome of ACL reconstruction. Previous studies demonstrated that supervised rehabilitation increased functional performance and return to sport rate after ACL surgery (29,30). The importance of timing of return to sport has been represented by the remodeling process of the graft (31). The remodeling process consists of three phases and the restructuring towards the properties of an intact ACL takes more than 6 months after reconstruction (31). Furthermore, Grindem et al. showed that a delay in return to sport from 6 to 9 months after ACL reconstruction decreased the risk of ACL injury (32). In addition, ACL injuries have shown to predict worse patient reported knee function after ACL reconstruction compared to patients without injury (33,34).

In the present study, sport participation rates were higher in satisfied compared to unsatisfied patients. Nwachukwu et al. also found associations between return to sport and PS after ACL reconstruction (35). However, surgical reconstructions were performed by twenty-four surgeons using different grafts such as hamstring autograft, patellar tendon autograft and allograft (35). Therefore, our single-center, single-surgeon study, using hamstring autograft for ACL reconstruction, adds evidence on the importance of return to sport for PS. Furthermore, the present study found that patient reported knee function and quality of life was associated with PS. The International Documentation Committee (IKDC) score, the EuroQol-5 Domain and the EuroQol-Visual Analogue Scale were higher in satisfied compared to unsatisfied patients. Kocher et al. evaluated 201 patients at a median of 2.9 years after primary ACL surgery (10). Higher Lysholm and IKDC scores corresponded to higher PS with the outcome after ACL reconstruction (10). Ardern et al. assessed 170 patients at an average of 3 years following ACL surgery (6). Higher Knee Osteoarthritis Outcome Scores and Quality of Life scales were found in patients who were satisfied with the knee function after ACL reconstruction (6).

The present study has several limitations. Firstly, this study has a retrospective design with risk of recall bias at final follow-up. However, the present study is one of the few studies evaluating predictors of PS after primary ACL reconstruction. Secondly, patients not participating in level I or II sports prior to ACL injury were excluded. Therefore, the results of the present study may not be generalizable to physically inactive patients

before ACL injury. However, this study included physically active patients before ACL injury to ensure a representative sample of patients undergoing ACL reconstruction (36). Thirdly, all patients underwent primary hamstring ACL reconstruction performed by one experienced orthopedic surgeon. Studies have shown that graft type predicts pain, functional performance and return to sport after ACL reconstruction (37,38). In addition, experienced ACL surgeons showed superior results compared to inexperienced ACL surgeons (39). Therefore, the results may not be generalizable to all patients undergoing ACL reconstruction. Yet, the aim of the present study was to evaluate predictors of PS following primary hamstring ACL surgery. In addition, the single-center, single-surgeon design prevented the influence of surgery and hospital care on PS (39-41). Fourthly, patient expectations and postoperative knee symptoms were not assessed in the present study. Patient expectations and postoperative knee symptoms (e.g. swelling, stiffness) have shown to predict PS after ACL reconstruction (9,10). Nevertheless, the present study provided important insights about the role of supervised postoperative rehabilitation, timing of return to pre-injury level of sport and ACL injury on PS after ACL surgery. Lastly, PS measurement has not been standardized (7). Therefore, the present study used the most common measurement methods (binary and numerical scales) to assess PS after ACL reconstruction (7).

In conclusion, the present study provided data on predictors of PS after primary hamstring ACL reconstruction. Furthermore, PS was associated with pre-injury level of sport participation, patient reported knee function and quality of life. The results of the present study might be used to counsel patients about expectations after primary hamstring ACL reconstruction.

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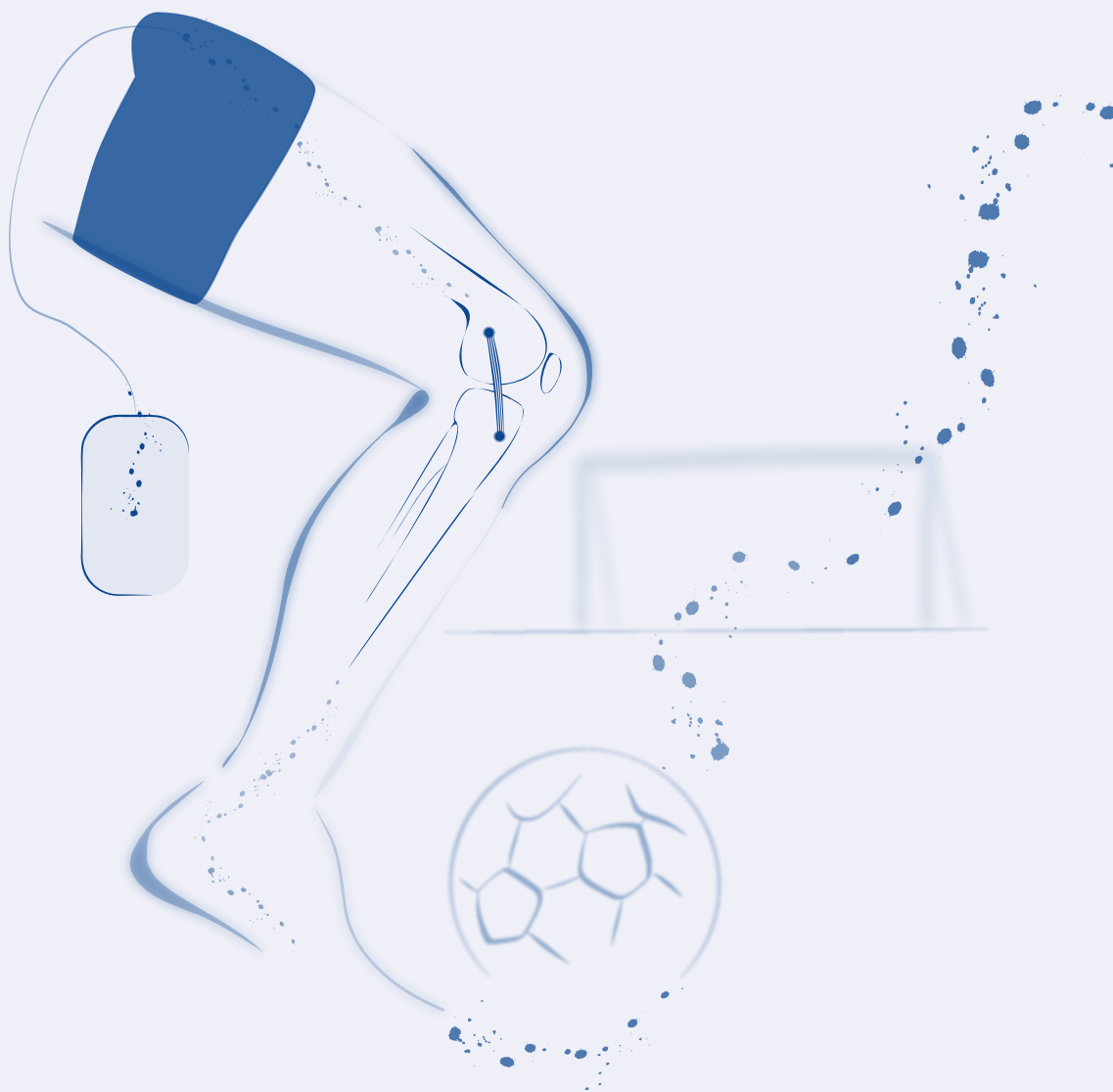




# Part III

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Low-load BFR training post-ACL surgery



# Chapter 4

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## **Effect of low-load blood flow restriction training after anterior cruciate ligament reconstruction: a systematic review**

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## Abstract

**Background:** Quadriceps strength and mass deficits are common after anterior cruciate ligament (ACL) reconstruction. Postoperatively, heavy load resistance training can have detrimental effects on knee joint pain and ACL graft laxity. Therefore, low-load blood flow restriction (LL-BFR) training has been suggested as an alternative to traditional strength rehabilitation.

**Purpose:** The present systematic review aimed to investigate the effect of LL-BFR training on quadriceps strength, quadriceps mass, knee joint pain, and ACL graft laxity after ACL reconstruction compared to non-BFR training.

**Study design:** Systematic review

**Methods:** A systematic literature search of PubMed, EMBASE.com, Cochrane Library/Wiley, CINAHL/Ebsco and Web of Science/Clarivate Analytics was performed on 19 February 2021. Studies were included if they compared LL-BFR and non-BFR training after ACL reconstruction with pre- and post-intervention quadriceps strength, quadriceps mass, knee joint pain or ACL graft laxity measurement. Systematic reviews, editorials, case reports and studies not published in a scientific peer reviewed journal were excluded. The risk of bias of randomized studies was assessed with the use of the Cochrane Risk of Bias Tool.

**Results:** A total of six randomized controlled trials were included. Random sequence generation and allocation concealment was defined as high risk in two of the six studies. In all studies blinding of participants and personnel was unclear or could not be performed. The included studies used different LL-BFR and non-BFR protocols with heterogeneous outcome measurements. Therefore, a qualitative analysis was performed. Two of the six studies assessed quadriceps strength and demonstrated significant greater quadriceps strength after LL-BFR compared to non-BFR training. Quadriceps mass was evaluated in four studies. Two studies observed significant greater quadriceps mass after LL-BFR compared to non-BFR training, while two studies observed no significant difference in quadriceps mass. Knee joint pain was assessed in three studies with significantly less knee joint pain after LL-BFR compared to non-BFR training. Two studies evaluated ACL graft laxity and observed no significant difference in ACL graft laxity between LL-BFR and non-BFR training.

**Conclusion:** The results of this systematic review indicate that LL-BFR training after ACL reconstruction may be beneficial on quadriceps strength, quadriceps mass, and knee joint pain compared to non-BFR training with non-detrimental effects on ACL graft laxity. However, more randomized controlled trials with standardized intervention protocols and outcome measurements are needed to add evidence on the clinical value of LL-BFR training.

## Introduction

Quadriceps strength and mass deficits are common after anterior cruciate ligament (ACL) reconstruction (1-6). Approximately 30% of patients have quadriceps strength deficits 12 months after ACL surgery (1,3). Quadriceps mass deficits can be as high as 30% and can persist for many years after ACL reconstruction (5). Furthermore, quadriceps mass deficits can negatively affect quadriceps strength (7-9). This is of importance as quadriceps strength after ACL reconstruction is associated with patient reported outcome measurements, functional performance, return to sport and ACL re-injury (1,10-16). Therefore, interventions to address quadriceps strength and mass deficits after ACL reconstruction are imperative.

Heavy load resistance (HLR) training using external loads >60% of one repetition maximum (1RM) is recommended to increase quadriceps strength and mass (17). However, after ACL reconstruction, training with external loads >60% 1RM can have detrimental effects on knee joint pain and ACL graft laxity (18-23). Therefore, low-load blood flow restriction (LL-BFR) training using external loads of 20-40% 1RM has been suggested as an alternative to traditional strength rehabilitation (24,25). During LL-BFR training, a pressurized cuff is applied to the proximal thigh that occludes venous outflow while maintaining arterial inflow (24,25). The combination of venous occlusion and resistance training is believed to induce muscle hypertrophy secondary to elevated systematic hormone production, cell swelling, production of reactive oxygen species, intramuscular anabolic signaling and fast-twitch fiber recruitment (25-27).

A recent systematic review showed promising results of LL-BFR training on quadriceps mass after ACL reconstruction (28). As LL-BFR training is an increasingly popular method for the rehabilitation after an ACL reconstruction, it is important to evaluate the value of this treatment (24,25). Therefore, the present systematic review aimed to investigate the effect of LL-BFR training on quadriceps strength, quadriceps mass, knee joint pain and ACL graft laxity after ACL reconstruction compared to non-BFR training.

## Materials and methods

The review protocol was registered on PROSPERO (CRD42020163467) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (29).

### Search strategy and study selection

A systematic literature search in PubMed, EMBASE.com, Cochrane Library/Wiley, CINAHL/Ebsco and Web of Science/Clarivate Analytics was performed on 19 February 2021 (BK, MH). The following search terms, including all synonyms, were used to search in all

databases as index term and as free-text words: blood flow restriction and anterior cruciate ligament (See Appendix 1 for the detailed search strategy). The results of the literature search were collected in the reference management program RefWorks and were de-duplicated (30). Studies were included if they compared LL-BFR and non-BFR training after ACL reconstruction with pre- and post-intervention quadriceps strength or quadriceps mass or knee joint pain or ACL graft laxity measurement. Non-BFR training was defined as strength training without vascular restriction. The exclusion criteria were: systematic reviews, editorials, case reports and studies not published in a scientific, peer reviewed journal. Two reviewers (BK and AT) separately and independently screened all titles and abstracts. The full text was reviewed if title and abstract suggested a study of interest. In case of disagreement, consensus was achieved by a third researcher (MS). In addition, trial reference lists of included studies were screened for relevant articles.

Appendix 1. Detailed search strategy.

| PubMed |                                                                                                                                                                                                                                                                                                                                              |         |
|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Search | Query                                                                                                                                                                                                                                                                                                                                        | Results |
| #9     | #4 AND #8                                                                                                                                                                                                                                                                                                                                    | 266     |
| #8     | #5 OR #6 OR #7                                                                                                                                                                                                                                                                                                                               | 207.837 |
| #7     | Occlusion*[tiab] OR "blood flow restricti*[tiab] OR blood vessel restricti*[tiab] OR kaatsu[tiab] OR BFR[tiab] OR BFRT[tiab] OR "ischemic Precondition*[tiab] OR "Ischemic Pre Condition*[tiab]                                                                                                                                              | 168.260 |
| #6     | "Ischemic Preconditioning"[Mesh]                                                                                                                                                                                                                                                                                                             | 8.354   |
| #5     | "Therapeutic Occlusion"[Mesh]                                                                                                                                                                                                                                                                                                                | 43.043  |
| #4     | #1 OR #2 OR #3                                                                                                                                                                                                                                                                                                                               | 88.235  |
| #3     | "Anterior Cruciate Ligament*[tiab] OR "Anterior Cranial Cruciate Ligament*[tiab] OR "Cranial Cruciate Ligament*[tiab] OR ACL[tiab] OR ACLR[tiab] OR anterior cruciate knee ligament*[tiab] OR musculoskeletal*[tiab] OR "locomotor apparatus*[tiab] OR "locomotor system*[tiab] OR "locomotory apparatus*[tiab] OR "locomotory system*[tiab] | 84.258  |
| #2     | "Musculoskeletal System"[Mesh:NoExp]                                                                                                                                                                                                                                                                                                         | 4.877   |
| #1     | "Anterior Cruciate Ligament"[Mesh] OR "Anterior Cruciate Ligament Reconstruction"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh]                                                                                                                                                                                                       | 16.428  |

[Mesh], Medical Subject Headings; [tiab], words in title or abstract.

**EMBASE.com**

| Search | Query                                                                                                                                                                                                                                                                                                                                                        | Results |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| #11    | #6 AND #10                                                                                                                                                                                                                                                                                                                                                   | 725     |
| #10    | #7 OR #8 OR #9                                                                                                                                                                                                                                                                                                                                               | 335-952 |
| #9     | occlusion*:ab,ti OR 'blood flow restricti*':ab,ti OR 'blood vessel restricti*':ab,ti OR kaatsu:ab,ti OR bfr:ab,ti OR bfr*:ab,ti OR 'ischemic precondition*':ab,ti OR 'ischemic pre condition*':ab,ti                                                                                                                                                         | 227.465 |
| #8     | 'ischemic preconditioning'/exp                                                                                                                                                                                                                                                                                                                               | 7.371   |
| #7     | 'blood vessel occlusion'/exp                                                                                                                                                                                                                                                                                                                                 | 171.767 |
| #6     | #1 OR #2 OR #3 OR #4 OR #5                                                                                                                                                                                                                                                                                                                                   | 159.345 |
| #5     | ((('anterior cruciate ligament*' NEAR/3 knee*):ab,ti) OR 'anterior cruciate ligament*' OR 'anterior cranial cruciate ligament*':ab,ti OR 'cranial cruciate ligament*':ab,ti OR musculoskeletal*:ab,ti OR 'locomotor apparatus*':ab,ti OR 'locomotory apparatus*':ab,ti OR 'locomotor system*':ab,ti OR 'locomotory system*':ab,ti OR acl:ab,ti OR acl*:ab,ti | 120.676 |
| #4     | 'anterior cruciate ligament reconstruction'/exp                                                                                                                                                                                                                                                                                                              | 11.309  |
| #3     | 'musculoskeletal system'/de                                                                                                                                                                                                                                                                                                                                  | 43.795  |
| #2     | 'anterior cruciate ligament injury'/exp                                                                                                                                                                                                                                                                                                                      | 10.451  |
| #1     | 'anterior cruciate ligament'/exp                                                                                                                                                                                                                                                                                                                             | 12.122  |

/exp, emtree keywords with explosion; /de, emtree keywords without explosion; :ab,ti, words in title or abstract.

**Cochrane Library/Wiley**

| Search | Query                                                                                                                                                                                                                                                                                                                                    | Results |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| #3     | #1 AND #2                                                                                                                                                                                                                                                                                                                                | 99      |
| #2     | ((Occlusion* OR "Ischemic Precondition*" OR "Ischemic Pre Condition*" OR "blood flow restricti*" OR "blood vessel restricti*" OR kaatsu OR BFR OR BFR*)):ti,ab,kw (Word variations have been searched)                                                                                                                                   | 14.077  |
| #1     | ((("Anterior Cruciate Ligament*" OR "Anterior Cranial Cruciate Ligament*" OR "Cranial Cruciate Ligament*" OR ACL OR ACL * OR "anterior cruciate knee ligament*" OR musculoskeletal* OR "locomotor apparatus*" OR "locomotor system*" OR "locomotory apparatus*" OR "locomotory system*"))):ti,ab,kw (Word variations have been searched) | 17.021  |

Ti,ab,kw, words in title, abstract or keyword.

**CINAHL/Ebsco**

| Search | Query                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Results |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| #10    | #4 AND #9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 81      |
| #9     | #5 OR #6 OR #7 OR #8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 24.978  |
| #8     | AB occlusion* OR "Ischemic Precondition*" OR "Ischemic Pre Condition*" OR "blood flow restricti*" OR "blood vessel restricti*" OR Kaatsu OR BFR OR BFR*                                                                                                                                                                                                                                                                                                                                                                                                                                        | 20.806  |
| #7     | TI occlusion* OR "Ischemic Precondition*" OR "Ischemic Pre Condition*" OR "blood flow restricti*" OR "blood vessel restricti*" OR Kaatsu OR BFR OR BFR*                                                                                                                                                                                                                                                                                                                                                                                                                                        | 8.799   |
| #6     | "therapeutic occlusion"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 10      |
| #5     | (MH "Ischemic Preconditioning")                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 309     |
| #4     | #1 OR #2 OR #3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 43.045  |
| #3     | TI ( ("Anterior Cruciate Ligament*" OR "Anterior Cranial Cruciate Ligament*" OR "Cranial Cruciate Ligament*" OR ACL OR ACL* OR "anterior cruciate knee ligament*" OR musculoskeletal* OR "locomotor apparatus*" OR "locomotor system*" OR "locomotory apparatus*" OR "locomotory system*" ) ) OR AB ( ("Anterior Cruciate Ligament*" OR "Anterior Cranial Cruciate Ligament*" OR "Cranial Cruciate Ligament*" OR ACL OR ACL* OR "anterior cruciate knee ligament*" OR musculoskeletal* OR "locomotor apparatus*" OR "locomotor system*" OR "locomotory apparatus*" OR "locomotory system*" ) ) | 40.133  |
| #2     | MH musculoskeletal system                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 3.660   |
| #1     | MH anterior cruciate ligament OR MH anterior cruciate ligament injuries OR MH anterior cruciate ligament reconstruction                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 11.120  |

MH, Mapped Heading, keyword; TI, words in title; AB, words in abstract.

**Web of Science/ Clarivate Analytics**

| Search | Query                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Results |
|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| #3     | #2 AND #1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 303     |
| #2     | Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years<br>TOPIC: (occlusion*) OR TOPIC: ("blood flow restricti*") OR TOPIC: ("blood vessel restricti*") OR TOPIC: (kaatsu) OR TOPIC: (BFR) OR TOPIC: (BFR*) OR TOPIC: ("ischemic precondition*") OR TOPIC: ("ischemic pre condition*")                                                                                                                                                                                                                                           | 175.657 |
| #1     | Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years<br>TOPIC: ("anterior cruciate ligament*") OR TOPIC: ("anterior cranial cruciate ligament*") OR TOPIC: ("cranial cruciate ligament*") OR TOPIC: (ACL) OR TOPIC: (ACL*) OR TOPIC: ("anterior cruciate knee ligament*") OR TOPIC: ("locomotor apparatus*") OR TOPIC: ("locomotory apparatus*") OR TOPIC: ("locomotor system*") OR TOPIC: ("locomotory system*") OR TOPIC: (musculoskeletal*)<br>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years | 102.430 |

TOPIC, words in title, abstract or keyword.

## Data extraction

Data of included articles were extracted with the use of RevMan 5.4 (Review Manager 5.4, The Cochrane Centre Collaboration, Copenhagen, Denmark, 2020) including: year of publication, study design, number of patients, study arms, graft used for ACL reconstruction, patient characteristics, LL-BFR training protocol, non-BFR training protocol, and quadriceps strength, quadriceps mass, knee joint pain, and ACL graft laxity measurements (31). When raw data of outcome measurements were not available, the authors were contacted to provide raw data.

## Study quality and reporting

The independent reviewers (BK and AT) assessed the risk of bias of the included studies with the use of the Cochrane Risk of Bias Tool. Non-randomized studies were assessed with the ROBINS-I checklist (32). The included studies were evaluated on: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.

## Data synthesis

Outcome measurements were extracted with the use of RevMan 5.4 (31). The difference in pre- and post-intervention mean and standard deviation (SD) was used to calculate the standardized mean difference (SMD). In case SD was not available, this was estimated in accordance with recommendations provided by Cochrane Handbook for Systematic Reviews (33). Data were pooled for a meta-analysis if the included studies were clinically, methodologically and statistically homogenous. In case of considerable heterogeneity ( $I^2 > 75\%$ ) of the study results, a qualitative analysis was performed (34). The level of statistical significance was set at  $p \leq 0.05$ .

# Results

## Study selection and characteristics

The database search yielded 1474 articles. After initial title and abstract screening, 11 articles were assessed for eligibility. The remaining 11 articles were fully read and six articles met the inclusion criteria. The two independent reviewers agreed on selection of eligible studies and achieved consensus on which studies to include. No additional studies were identified through reference list screening. Therefore, six articles were included in the systematic review (Figure 1). Table 1 shows an overview of the study characteristics.

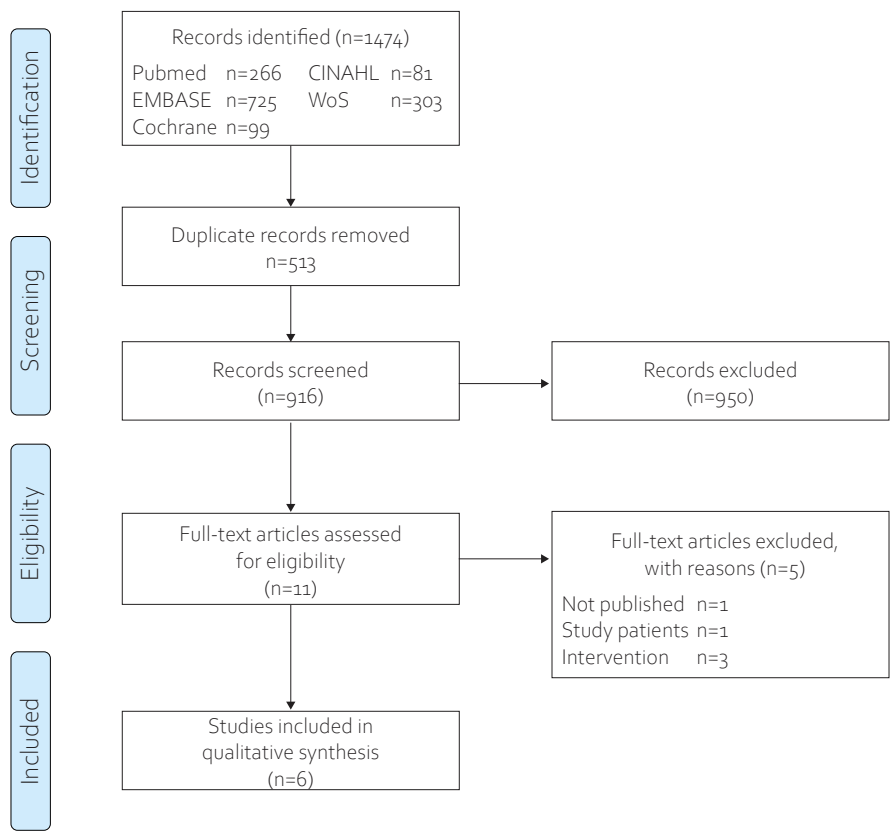


Figure 1. Flow chart of the literature search and selection procedure.

**Table 1.** Overview of study characteristics.

| Author (Year)   | Study design                | Total number of patients | Study arms (No.)                            | Outcome                                                                       |
|-----------------|-----------------------------|--------------------------|---------------------------------------------|-------------------------------------------------------------------------------|
| Hughes (2019a)  | Randomized controlled trial | 24                       | LL-BFR group (n=12)<br>Non-BFR group (n=12) | Quadriceps strength<br>Quadriceps mass<br>Knee joint pain<br>ACL graft laxity |
| Hughes (2019b)  | Randomized controlled trial | 24                       | LL-BFR group (n=12)<br>Non-BFR group (n=12) | Knee joint pain                                                               |
| Hughes (2018)   | Randomized controlled trial | 20                       | LL-BFR group (n=10)<br>Non-BFR group (n=10) | Knee joint pain                                                               |
| Iversen (2014)  | Randomized controlled trial | 24                       | LL-BFR group (n=12)<br>Non-BFR group (n=12) | Quadriceps mass                                                               |
| Ohta (2003)     | Randomized controlled trial | 44                       | LL-BFR group (n=22)<br>Non-BFR group (n=22) | Quadriceps strength<br>Quadriceps mass<br>ACL graft laxity                    |
| Takarada (2000) | Controlled trial            | 16                       | LL-BFR group (n=8)<br>Non-BFR group (n=8)   | Quadriceps mass                                                               |

LL-BFR: Low-load blood flow restriction.

Three studies were conducted in the United Kingdom, two in Japan and one in Norway (18, 35-39). The studies conducted in the United Kingdom are three reports from the same study (18, 35,36). However, the three reports from the same study described different outcome measurements, thus, were included in this review. The included studies involved a total of 152 patients who had been randomized into LL-BFR (n=76) or non-BFR (n=76) group (18,35-39). Sample sizes ranged between 16 and 44 patients (18,35-39). Five studies used hamstring graft for ACL reconstruction, whereas one study did not report type of graft (18,35-39). Patient characteristics were not statistically significant different between the LL-BFR and non-BFR group. Table 2 shows an overview of the patient characteristics.

**Table 2.** Overview of patient characteristics.

| Author (Year)   | Graft for ACL reconstruction | Male in LL-BFR & non-BFR group | Age (years) in LL-BFR & non-BFR group | Weight (kg) in LL-BFR & non-BFR group | BMI in LL-BFR & non-BFR group |
|-----------------|------------------------------|--------------------------------|---------------------------------------|---------------------------------------|-------------------------------|
| Hughes (2019a)  | Hamstring                    | 7 (58%) & 10 (83%)             | 29 (7) & 29 (7)                       | 76 (15) & 79 (15)                     | 25.4 (3.9) & 26.4 (4.4)       |
| Hughes (2019b)  | Hamstring                    | 7 (58%) & 10 (83%)             | 29 (7) & 29 (7)                       | 76 (15) & 79 (15)                     | 25.4 (3.9) & 26.4 (4.4)       |
| Hughes (2018)   | Hamstring                    | 6 (60%) & 7 (70%)              | 29 (5) & 31 (7)                       | 77 (16) & 81 (12)                     | 25.7 (4.2) & 23.5 (3.4)       |
| Iversen (2014)  | Hamstring                    | 7 (58%) & 7 (58%)              | 25 (7) & 30 (9)                       | 77 (12) & 78 (10)                     | -                             |
| Ohta (2003)     | Hamstring                    | 13 (59%) & 12 (55%)            | 28 (10) & 30 (10)                     | 65 (14) & 63 (9)                      | -                             |
| Takarada (2000) | -                            | 4 (50%) & 4 (50%)              | 22 (1) & 23 (1)                       | 59 (1) & 62 (2)                       | -                             |

Results are presented as numbers (percentage) or mean (SD). ACL: anterior cruciate ligament; BMI: body mass index; LL-BFR: low-load blood flow restriction.

## LL-BFR and non-BFR protocols

The intervention protocols are shown in Table 3. The duration of the intervention varied from 11 days up to 14 weeks and training sessions varied from two sessions/week up to two sessions/day (18,35-39). LL-BFR training was used in combination with low-load leg press, leg extension or straight leg raise exercises (18,35-39). The external load varied from body weight up to 30% 1RM and was not specified in two studies (18,35-39). Automatic personalized tourniquet systems and pneumatic cuffs were used during LL-BFR training (18,35-39). The occlusion pressure ranged between 148 and 238 mmHg, while cuff width ranged from 9 to 14 cm (18,35-39). In three studies LL-BFR pressure was defined as 80% of the limb occlusion pressure (ranged from 140 to 160 mmHg), whereas the occlusion pressure was based on previous research in three studies (ranged from 180 to 240mmHg) (18,35-39). LL-BFR was intermittently applied with reperfusion periods ranging from 30 to 180 seconds (18,35,36,38,39). In three studies, non-BFR training consisted of the same exercise protocol as LL-BFR training but without vascular restriction (37-39). Hughes et al. used different exercise protocols in the non-BFR and LL-BFR group (18,35,36). In the non-BFR group, the patients performed three sets of 10 repetitions using external loads of 70% 1RM. In the LL-BFR group, the patients performed four sets (30-15-15-15) using external loads of 30% 1RM (18,35,36).

**Table 3.** Overview of intervention.

| Author (Year)   | BFR device                               | Cuff width | BFR pressure                                                   | LL-BFR training                                                                                               | Non-BFR training                                                                                           | Exercises                                                                                                              | Duration                                                  | Total training sessions |
|-----------------|------------------------------------------|------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------|
| Hughes (2019a)  | Automatic personalized tourniquet system | 11.5 cm    | Mean 150 mmHg<br>Based on 80% of LOP                           | 4 sets (30-15-15-15 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 30% 1RM<br>Session: 2x/week | 3 sets (10-10-10 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 70% 1RM<br>Session: 2x/week | Unilateral leg press                                                                                                   | 8 weeks<br>Start: 2 weeks postop<br>End: 10 weeks postop  | 16                      |
| Hughes (2019b)  | Automatic personalized tourniquet system | 11.5 cm    | Mean 150 mmHg<br>Based on 80% of LOP                           | 4 sets (30-15-15-15 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 30% 1RM<br>Session: 2x/week | 3 sets (10-10-10 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 70% 1RM<br>Session: 2x/week | Unilateral leg press                                                                                                   | 8 weeks<br>Start: 2 weeks postop<br>End: 10 weeks postop  | 16                      |
| Hughes (2018)   | Automatic personalized tourniquet system | 11.5 cm    | Mean 148 mmHg<br>Based on 80% of LOP                           | 4 sets (30-15-15-15 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 30% 1RM<br>Session: 2x/week | 3 sets (10-10-10 reps)<br>Inter-set rest periods: 30 seconds<br>External load: 70% 1RM<br>Session: 2x/week | Unilateral leg press                                                                                                   | 8 weeks<br>Start: 2 weeks postop<br>End: 10 weeks postop  | 16                      |
| Iversen (2014)  | Contoured pneumatic occlusion cuff       | 14 cm      | Start: 130 mmHg<br>End: 180 mmHg<br>Based on previous research | 5 sets of 20 reps<br>Inter-set rest periods: 3 minutes<br>External load: low<br>Session: 2x/day               | 5 sets of 20 reps<br>Inter-set rest periods: 3 minutes<br>External load: low<br>Session: 2x/day            | Isometric quadriceps contraction progressing to leg extension over a knee-roll and straight leg raise                  | 12 days<br>Start: 2 days postop<br>End: 14 days postop    | 24                      |
| Ohta (2003)     | Hand-pumped air tourniquet               | -          | 180 mmHg<br>Based on previous research                         | 1-3 sets (20 reps)<br>Inter-set rest periods: unknown<br>External load: 0-14 kg<br>Session: 6x/week           | 1-3 sets (20 reps)<br>Inter-set rest periods: unknown<br>External load: 0-14 kg<br>Session: 6x/week        | Straight leg raise, hip joint abduction/adduction, half squat, step up, elastic tube and knee-bending walking exercise | 14 weeks<br>Start: 2 weeks postop<br>End: 16 weeks postop | 84                      |
| Takarada (2000) | Pneumatic occlusion cuff                 | 9 cm       | Start: 180 mmHg<br>End: 238 mmHg<br>Based on previous research | 5 sets<br>Inter-set rest periods: 3 minutes<br>External load: low<br>Session: 2x/day                          | 5 sets<br>Inter-set rest periods: 3 minutes<br>External load: low<br>Session: 2x/day                       | Hospital rehabilitation protocol with knee brace immobilization                                                        | 11 days<br>Start: 3 days postop<br>End: 14 days postop    | 22                      |

LL-BFR: low-load blood flow restriction; LOP: limb occlusion pressure; 1RM: one repetition maximum; Postop: postoperatively; Reps: repetitions.

Risk of bias

An overview of the quality assessment of the included studies is reported in Figure 2. Random sequence generation and allocation concealment was defined as high risk for bias in two of the six studies. In all studies blinding of participants and personnel was unclear or could not be performed.

|               | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|---------------------------------------------|-----------------------------------------|-----------------------------------------------------------|-------------------------------------------------|------------------------------------------|--------------------------------------|------------|
| 2000 Takarada | -                                           | -                                       | ?                                                         | ?                                               | +                                        | +                                    | +          |
| 2003 Ohta     | -                                           | -                                       | ?                                                         | ?                                               | +                                        | +                                    | +          |
| 2014 Iversen  | +                                           | +                                       | ?                                                         | +                                               | +                                        | +                                    | +          |
| 2018 Hughes   | +                                           | +                                       | -                                                         | +                                               | +                                        | +                                    | +          |
| 2019a Hughes  | +                                           | +                                       | -                                                         | +                                               | +                                        | +                                    | +          |
| 2019b Hughes  | +                                           | +                                       | -                                                         | +                                               | +                                        | +                                    | +          |

Figure 2. Review authors’ judgements about each risk of bias domain with the use of the Cochrane Risk of Bias Tool.

Heterogeneity

Comorbidities and concomitant injuries of study participants were not defined in the included studies. Furthermore, different LL-BFR and non-BFR protocols with heterogeneous outcome measurements were used. Therefore, only a qualitative analysis was performed.

## Outcome measurements

### Quadriceps strength

Quadriceps strength was evaluated in two studies by measuring RM, isokinetic contraction at 60°/seconds, isokinetic contraction at 150°/seconds, isokinetic contraction at 180°/seconds, isokinetic contraction at 300°/seconds or isometric contraction at 60° knee flexion (35,37). Quadriceps strength was measured pre-operatively and at nine up to 16 weeks postoperatively (35,37). Ohta et al. showed significantly less strength deficits in isokinetic knee extension at 60°/seconds ( $p<0.001$ ), isokinetic knee extension at 180°/seconds ( $p=0.004$ ) and isometric contraction at 60° knee flexion ( $p<0.001$ ) after LL-BFR compared to non-BFR training (37). Hughes et al. reported significantly less strength deficits in isokinetic knee extension at 150° and 300°/seconds after LL-BFR compared to non-BFR training ( $p=0.010$ ) (35). However, no significant differences in RM ( $p=0.220$ ) and isokinetic knee extension at 60°/seconds ( $p=0.200$ ) were observed between LL-BFR and non-BFR training (35).

### Quadriceps mass

Three studies used MRI to measure changes in quadriceps cross-sectional area (CSA), while one study used ultrasound to measure changes in vastus lateralis muscle thickness (35,37-39). Quadriceps mass was measured pre-operatively and 14 days up to 16 weeks postoperatively (35,37-39). Takarada et al. showed significant less reduction in quadriceps CSA after LL-BFR compared to non-BFR training ( $p=0.046$ ) (38). Ohta et al. reported a significant increase in quadriceps CSA after 14 weeks LL-BFR compared to non-BFR training ( $p=0.040$ ) (37). Iversen et al. concluded that there was no significant difference in quadriceps CSA between LL-BFR and non-BFR training ( $p=0.626$ ) (39). Hughes et al. used ultrasound to assess changes in vastus lateralis muscle thickness and demonstrated no significant difference in quadriceps increase between LL-BFR and non-BFR training ( $p=0.230$ ) (35).

### Knee joint pain

Knee joint pain was assessed using a numerical rating scale in two studies, while one study used the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain score (18,35,36). Knee joint pain was evaluated following each session, 24h post-exercise or 10 weeks postoperatively (18,35,36). Two studies observed significant lower knee joint pain scores in LL-BFR compared to non-BFR training (18,36). Furthermore, one study showed significant greater increase in KOOS pain score after LL-BFR compared to non-BFR training (35).

### ACL graft laxity

Two studies used a knee ligament arthrometer to measure changes in ACL graft laxity (35,37). ACL graft laxity was measured pre-operatively and at 10 up to 16 weeks postoperatively. No significant difference in ACL graft laxity was observed between LL-BFR and non-BFR (35,37).

## Discussion

The most important finding of the present systematic review was that low-load blood flow restriction (LL-BFR) training after anterior cruciate ligament (ACL) reconstruction may be beneficial on quadriceps strength and quadriceps mass compared to non-BFR training. Furthermore, LL-BFR training may decrease knee joint pain compared to non-BFR training with similar effects on ACL graft laxity. Thus, the present systematic review suggests that LL-BFR training may be an effective alternative to non-BFR training after an ACL reconstruction.

Regarding quadriceps strength, Ohta et al. showed less quadriceps strength deficits after LL-BFR compared to non-BFR training (37). In addition, Hughes et al. demonstrated similar and greater effects on quadriceps strength after LL-BFR compared to non-BFR training (35). Ohta et al. used low-load resistance training (LLR) training as non-BFR training, while Hughes et al. used heavy-load resistance training (HLR) training as non-BFR training. Therefore, the findings of the present review are consistent with current literature comparing LL-BFR training to LLR and HLR training in healthy and postoperative patients (40-46).

In regard to quadriceps mass, two studies demonstrated that LL-BFR training was more beneficial on quadriceps cross-sectional area (CSA) compared to non-BFR training (37,38). In contrast, Iversen et al. observed no difference in quadriceps CSA between LL-BFR and non-BFR training (39). The authors acknowledged that subtherapeutic training (e.g. training duration of 12 days) and LL-BFR application (e.g. no personalized BFR pressures) were possible reasons for this difference (39). Current evidence recommends training durations of 6-12 weeks and the use of personalized LL-BFR pressures (80% of limb occlusion pressure [LOP]) to achieve muscle strength and hypertrophy (23-25). In contrast to the previous studies, the non-BFR group of Hughes et al. did not consist of LLR but HLR training (35). In their study, ultrasound was used to examine vastus lateralis muscle thickness and no difference in muscle thickness was observed between LL-BFR and non-BFR training groups (35). Thus, the results of the present review are consistent with literature showing that LL-BFR training may be beneficial on quadriceps mass compared to LLR training and equally effective when compared to HLR training in healthy and postoperative patients (40-46).

The application of LL-BFR has generally been indicated for the elderly or injured/postoperative patients who cannot tolerate high external loads (43,47-50). This review adds evidence on the application of LL-BFR as three studies assessing pain observed improved pain relief with LL-BFR compared to non-BFR training in patients following ACL surgery (18,35,36). This is in contrast with a recent systematic review that observed no significant difference in pain relief between LL-BFR and non-BFR training in individuals

with knee joint pain (51). The study participants were heterogeneous and included individuals with patellofemoral pain, risk of symptomatic knee osteoarthritis, anterior knee pain and post knee arthroscopy (51). Furthermore, the heterogeneity in LL-BFR pressures and cuff width could explain the lack of effect on knee joint pain (51). Current evidence suggests that therapeutic restriction (defined as 80% of LOP) is achieved at lower LL-BFR pressures with wide compared to narrow cuffs (52-56). Furthermore, lower LL-BFR pressures are associated with less discomfort and greater safety (52-56). Thus, the use of non-personalized pressures without calculating the LOP may cause pain (53-56). In the present systematic review, all studies on knee joint pain used wide cuffs with an automatic personalized tourniquet system to calculate the LOP (18,35,36). Furthermore, all studies used HLR training as non-BFR training. Thus, pain relief may be the result of low external loads and hypoalgesia effects of LL-BFR training compared to HLR training (48,57,58).

A major challenge in the rehabilitation after an ACL reconstruction is optimizing muscle strength while minimizing mechanical stress to the knee joint (59-61). The importance is represented by the remodeling process of the ACL graft. The remodeling process consists of three phases and the restructuring towards the properties of an intact (non-injured) ACL takes more than six months after reconstruction (21,62). Thereby, accelerated rehabilitation protocols and high load resistance training may compromise graft remodeling and may result in increased ACL graft laxity (19-21,63). BFR training in combination with low external loads has the advantage of minimizing mechanical stress to the knee joint compared to HLR training (47,48). However, in the present systematic review only two studies evaluated ACL graft laxity and showed no significant difference on ACL graft laxity with LL-BFR compared to non-BFR training (35,37). Therefore, more randomized controlled trials are needed to evaluate the effect of LL-BFR training on ACL graft laxity compared to HLR training.

The present systematic review has several limitations. First of all, due to the heterogeneity in intervention protocols and outcome measurements no meta-analysis could be performed. Secondly, differences in LL-BFR and non-BFR protocols affect the results of the present systematic review. Three studies compared LL-BFR training to HLR training, while three other studies compared LL-BFR training to LLR training (18,35-39). Furthermore, three of the six studies used LL-BFR protocols as recommended by current evidence (18,35,36). Thirdly, blinding of participants and personnel could not be performed or was unclear in the included studies (18,35-39). This could affect the results, as the patients may have experienced a nonspecific effect or a placebo effect due to the novel nature of LL-BFR training. Overall, the methodological quality of the included studies ranged from moderate to good. Lastly, no long-term effects of LL-BFR training after ACL reconstruction were reported.

## Conclusion

The results of this systematic review indicate that LL-BFR training after ACL reconstruction may be beneficial on quadriceps strength, quadriceps mass, and knee joint pain compared to non-BFR training with non-detrimental effects on ACL graft laxity. However, more randomized controlled trials with operational definitions, standardized intervention protocols and outcome measurements are needed to add evidence on the clinical value of LL-BFR training.

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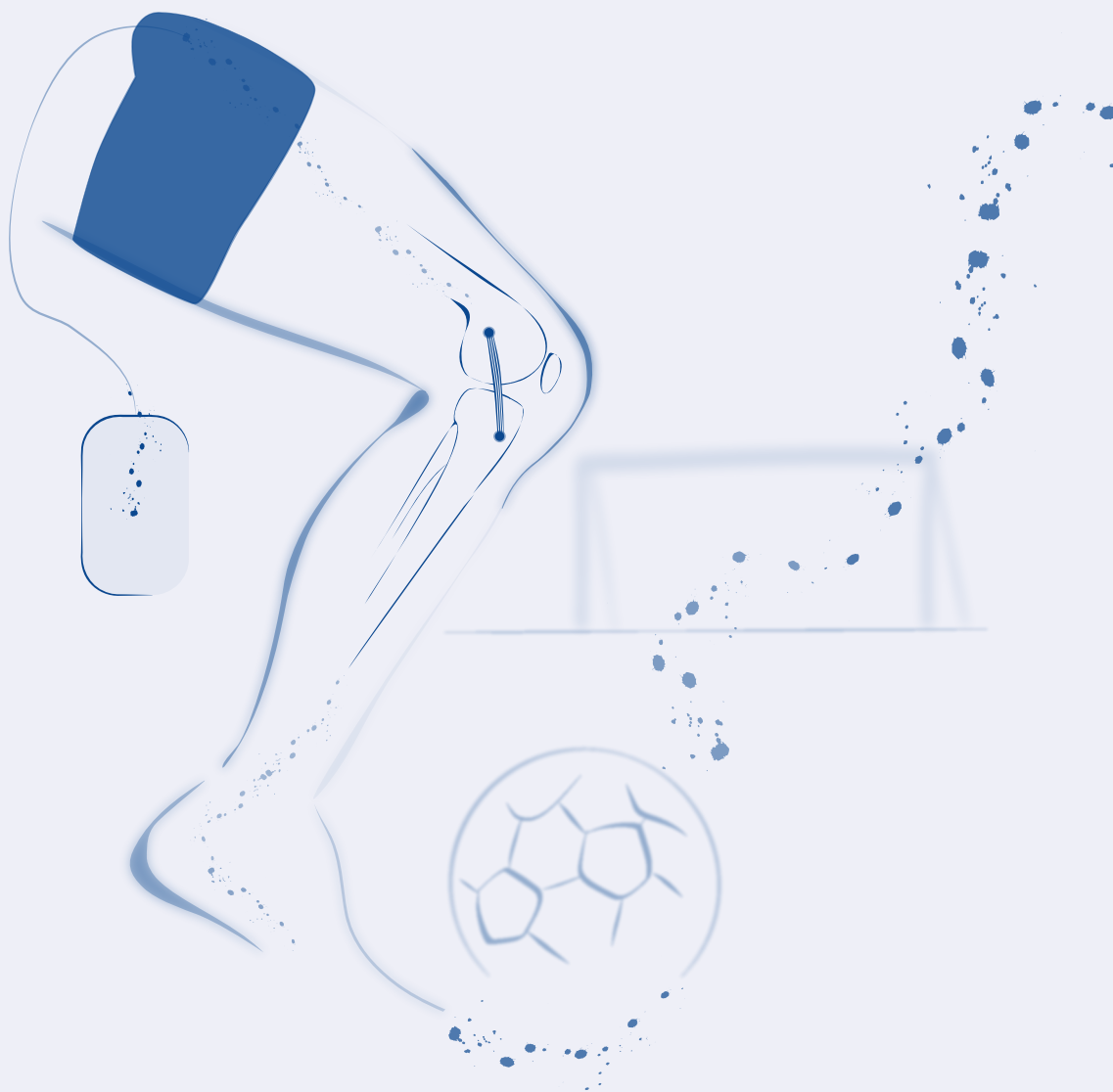
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# Chapter 5

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## **Low-load blood flow restriction training as a potential alternative to heavy-load resistance training in early-stage rehabilitation following bone-patellar tendon-bone ACL reconstruction: a randomized controlled trial**

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## Abstract

**Objective:** To compare the effects of low-load blood flow restriction training (LL-BFRT) and heavy-load resistance training (HLRT) on quadriceps and hamstring strength, knee pain, joint effusion, and range of motion following bone-patellar tendon-bone (BPTB) anterior cruciate ligament (ACL) reconstruction.

**Design:** Randomized controlled trial.

**Methods:** LL-BFRT and HLRT included 12 weeks of biweekly strength training. Quadriceps and hamstring strength, measured in Newton-meters per kilogram, was assessed at 60°/s, 180°/s and 300°/s at baseline and final follow-up. At final follow-up, knee pain, joint effusion, and range of motion deficits were assessed.

**Results:** Of 28 patients, 23 completed the study. Study groups were comparable at baseline. At final follow-up, no significant differences were observed in quadriceps strength at 60°/s (2.7 and 3.1,  $p=0.738$ , 180°/s (2.3 and 2.8,  $p=0.387$ ) and 300°/s (2.2 and 2.8,  $p=0.387$ ) as well as in hamstring strength at 60°/s (3.2 and 3.1,  $p=0.738$ ), 180°/s (3.2 and 2.9,  $p=0.738$ ) and 300°/s (2.8 and 2.6,  $p=0.738$ ) for the LL-BFRT and HLRT group, respectively. Similarly, no significant differences were found for knee pain (14.3% and 35.7%,  $p=0.380$ ), joint effusion (7.1% and 35.7%,  $p=0.444$ ), flexion deficit (7.1% and 28.6%,  $p=0.426$ ) and extension deficit (0.0% and 14.3%,  $p=0.478$ ).

**Conclusion:** LL-BFRT in early rehabilitation following BPTB ACL reconstruction demonstrated similar muscle strength, knee pain, joint effusion, and range of motion compared with HLRT. These results support LL-BFRT as a safe alternative when HLRT cannot be performed.

## Introduction

Rehabilitation following anterior cruciate ligament (ACL) reconstruction has evolved from a time-based to a criteria-based model (3-5,41,53). The aims of early-stage rehabilitation after ACL reconstruction are to address knee pain, decrease joint effusion, regain range of motion and restore muscle strength (4,41,53). Restoring muscle strength is particularly important, as deficits in muscle strength following ACL reconstruction are associated with reduced patient-reported knee function, increased kinesiophobia, and a lower likelihood of returning to pre-injury levels of sport participation (12,31,32,34,44,52). Currently, heavy-load resistance training (HLRT), using external loads of more than 60% of the one-repetition maximum (1RM), is recommended to stimulate muscle strength (30). However, concerns exist that HLRT following ACL reconstruction may have adverse effects on knee joint and ACL graft healing (10,16,40,43). Therefore, low-load blood flow restriction training (LL-BFRT), using external loads between 20 and 40% of 1RM, has been proposed as an alternative to HLRT (24,55). During LL-BFRT, a pressurized cuff is applied to the proximal thigh that occludes venous outflow while maintaining arterial inflow (24,55). This novel training modality has been reported safe and effective in healthy and postoperative patients (1,49,57). However, evidence regarding the effectiveness of LL-BFRT compared to HLRT following ACL reconstruction is limited (27). Hughes et al. and Vieira et al. reported that LL-BFRT in the early-stage rehabilitation following hamstring ACL reconstruction resulted in increased quadriceps and hamstring strength compared to HLRT with a greater reduction in knee pain (23,54). Additionally, Hughes et al. found that exercise adherence was high, with 91.2% of LL-BFRT and 87.5% of HLRT exercises being completed by patients (23). Interestingly, the role of LL-BFRT following ACL reconstruction using a bone-patellar tendon-bone (BPTB) autograft is unknown. This is particularly important to investigate, as the type of graft used can influence muscle strength and knee pain. Moreover, quadriceps strength deficits and knee pain are more common following BPTB ACL reconstruction compared to hamstring ACL reconstruction, whereas hamstring strength deficits are less common (6,37,48,58). The primary aim of this study was to evaluate the effects of LL-BFRT and HLRT on quadriceps and hamstring strength following BPTB ACL reconstruction. The secondary aims were to assess the impact of LL-BFRT and HLRT on knee pain, joint effusion, and range of motion, as well as exercise completion rates.

## Methods

This randomized controlled trial was approved by the medical ethical committee of Zuyderland Medical Center, Heerlen, the Netherlands (METCZ20190147). The study was registered in the Dutch National Trial Registry (OMON: Overview of Medical Research in the Netherlands) under registration number NL-OMON49262, on April 6, 2020. The trial

was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed consent before enrollment.

## Study patients

Patients undergoing primary BPTB ACL reconstruction at Zuyderland Medical Center, Sittard-Geleen, and scheduled for rehabilitation at Knie- heupcentrum plus, Sittard-Geleen were included in this study. Exclusion criteria were: any history of cardiovascular conditions, such as venous thromboembolism, sickle cell anemia, hypertension, or diabetes mellitus<sup>36</sup>. Patients who were unwilling or unable to participate were also excluded. Additionally, patients who underwent concomitant surgical interventions, such as cartilage or meniscus procedures, as well as collateral ligament repair or reconstruction, which contra-indicates accelerated postoperative rehabilitation, were excluded. Eligible patients were block-randomized (2:2) into either the LL-BFRT or HLRT group using a digital number generator (ResearchManager, Deventer, the Netherlands). Randomization and allocation were performed by an independent researcher.

## Surgical procedure

All patients received an ACL reconstruction using an autologous BPTB graft. The anteromedial portal was used to place the femoral tunnel in the isometric anteromedial bundle position, while the tibial tunnel was placed in the center of the native ACL footprint. This approach aligns with current concepts to ensure an anatomic tunnel placement and optimal ACL reconstruction<sup>2</sup>. Titanium interference screws (Zimmer Biomet, Indiana, USA) were used for femoral and tibial graft fixation. Additionally, lateral extra-articular tenodesis (modified Lemaire procedure) was performed in patients with preoperative high-grade pivot shift or hyperlaxity (≥6). The surgical procedures were performed by experienced ACL surgeons at Zuyderland Medical Center, Sittard-Geleen.

## Study intervention

All patients followed a criteria-based rehabilitation protocol at Knie- heupcentrum plus, Sittard-Geleen, under the supervision of physiotherapists specialized in ACL rehabilitation. Muscle strength training differed between the groups, depending on assignment of patients to either the LL-BFRT or HLRT protocol. Strength training (LL-BFRT or HLRT) started two weeks after surgery, when patients met the criteria to initiate strength training. These criteria included a knee range of motion of 0-90°, no or minimal effusion (defined as trace or 1+ based on the stroke test), and the ability to perform repeated straight leg raises without knee extension muscle lag (23,51). Patients who did not meet these criteria two weeks after surgery were reassessed at each training session until the requirements to initiate strength training were fulfilled. Once the criteria were met, biweekly strength training (LL-BFRT or HLRT) was started and continued until 14 weeks postoperatively.

The strength training program included leg press, leg extension, deadlift, and squat exercises, with 30-second inter-set rest periods and 120-180 seconds of rest between exercises. All exercises were standardized to ensure safety, reproducibility and controlled progression. The leg press was performed unilaterally on a Keiser A420 pneumatic machine (Keiser Corporation, Fresno (CA), United States of America) with knee flexion restricted to a maximum of 90°. The seated leg extension was performed unilaterally on a KINEO No Inertia Training (NIT) system (Globus, Codogne (TV), Italy), which provides constant resistance across the range of motion to ensure uniform muscle activation and precise control. Deadlifts were executed bilaterally using the conventional technique, beginning with kettlebell deadlifts and progressing to barbell deadlifts with a 20-kilogram bar. The squat exercises followed a comparable progression, starting with kettlebell squats and advancing to barbell back squats with a 20-kilogram bar. Squat depth was standardized to approximately 100° of knee flexion, corresponding to the thigh being parallel to the floor. Patients in the LL-BFRT group performed four sets of each exercise, consisting of 30, 15, 15, and 15 repetitions, respectively. Each exercise was performed at 30% of 1RM (23,24,55). Blood flow restriction was achieved using an automatic personalized tourniquet system (PTS) (MAD-UP, Angers, France), designed to automatically calculate limb occlusion pressure. Limb occlusion pressure (LOP) was defined as the minimum pressure required to achieve blood flow occlusion, ensuring acceptable accuracy and high reliability. The limb occlusion pressure was calculated in the position in which each exercise was performed. The PTS consisted of a dual-purpose, easy-fit variable contour nylon cuff (11.5x86 cm, 5 mm thick), connected by airtight hose tubing and automatically regulating pressure within acceptable limits. A LOP of 80% was applied during each exercise. The cuff was inflated throughout each exercise and was deflated during the 120-180 seconds of rest between exercises. Patients in the HLRT group performed three sets of each exercise (10, 10, 10 repetitions) at 70% of 1RM (23,24,55). In both groups, the 10RM strength was measured and used to predict 1RM strength (39). In addition, training load in both groups was increased by 10% if patients completed all repetitions in two consecutive strength training sessions.

## Primary outcome measurements

Isokinetic quadriceps (seated leg extension) and hamstring (standing leg curl) strength were measured using the Kineo Leg Pro (Globus, Codogne (TV), Italy) at two time points: two weeks before surgery and 14 weeks postoperatively. Muscle strength was normalized to body weight and expressed as Newton-meters per kilogram (Nm/kg). Following five submaximal warm-up repetitions and a three-minute rest period, patients performed three maximal-effort repetitions of knee extension and flexion throughout the full range of motion at 60°/s and 180°/s (23). Additionally, patients completed 10 maximal-effort repetitions at 300°/s, with a 20-second rest interval between speeds (23). The highest recorded value at each speed was used for analysis.

## Secondary outcome measurements

The secondary outcome measurements included knee pain, joint effusion, and range of motion, which were evaluated 14 weeks after surgery. An online survey tool (ResearchManager, Deventer, the Netherlands) was used to collect data on knee pain. Knee pain was assessed with the question: "Did you experience increased knee pain during the past 24 hours following strength training". Responses were recorded as yes or no. Assessment of joint effusion and range of motion was performed by an experienced physical therapist (TE). Joint effusion (yes/no) was evaluated 14 weeks postoperatively with the patient in a supine position, with the knee fully extended or as close to full extension as possible in case of an extension deficit (51). Passive knee range of motion was assessed 14 weeks after surgery using a long-arm goniometer, with the patient in a supine position (11). The presence of a flexion or extension deficit (yes/no) was recorded. A flexion deficit was defined as passive knee flexion of less than 125 degrees, and an extension deficit was defined as the inability to fully extend the knee (4). Exercise completion rates were calculated as the percentage of attended exercise sessions out of the total scheduled sessions for the LL-BFRT and HLRT group. Patients excluded before the start of the study intervention were not included in this calculation. Patient demographics (e.g., gender, pre-injury Tegner score) and operative details (e.g., meniscus injury, grade 3-4 chondral defect based on the International Cartilage Repair Society classification) were collected from the electronic medical records (13).

## Sample size calculation

The primary aim of this study was to compare muscle strength 14 weeks postoperatively between the LL-BFRT and HLRT groups. The sample size calculation used an expected effect size of 0.74 (Cohen's  $d$ ), based on previous studies (21,35). Using a two-sided test with a significance level ( $\alpha$ ) of 0.05 and a power ( $1-\beta$ ) of 0.95, a minimum of 12 patients per group was required to detect a meaningful difference in muscle strength. To account for a potential 10% dropout rate, 14 patients per group were needed. This calculation was performed using G\*Power version 3 (14).

## Data analysis

Statistical analyses were performed using SPSS Version 29.0 (IBM Corp, Chicago, IL, USA). An intention-to-treat analysis was conducted for all measurements. Categorical variables were compared using Chi-Square tests and presented as numbers and percentages. Continuous variables were tested for normality using the Shapiro-Wilk test. Parametric  $t$ -tests were used to analyze normally distributed data, which were reported as means and standard deviations (SD). Non-normally distributed data were reported as medians and interquartile ranges (IQR). For univariate nonparametric analysis, the Mann-Whitney  $U$  test was used for two-group comparisons. To account for multiple testing,  $p$ -values

were corrected using the Benjamini-Hochberg procedure to control the false discovery rate. Corrected p-values are presented, and a corrected p-value of  $<0.05$  was considered statistically significant.

## Results

### Study population

Baseline characteristics of the 28 included patients were analyzed using Chi-square tests for categorical variables and independent t-tests for continuous variables. No significant between-group differences were detected (Table 1). Of these 28 patients, 2 were excluded following surgery: one patient from the LL-BFRT group and one from the HLRT group, both due to the need for an additional chondral intervention, which was considered a contraindication. The remaining 26 patients met the criteria to begin strength training at two weeks post-surgery. During the study intervention, two patients from the LL-BFRT group were excluded: one due to pregnancy 10 weeks after ACL reconstruction and one due to dizziness occurring during the first LL-BFRT session at two weeks postoperatively. In the HLRT group, one patient was excluded due to a posttraumatic ipsilateral patellar fracture sustained in a bicycle accident six weeks after surgery (Figure 1).

**Table 1.** Baseline characteristics of study patients.

|                                                   | LL-BFRT group n=14 | HLRT group n=14 |
|---------------------------------------------------|--------------------|-----------------|
| Age in years, mean (SD)                           | 23.4 (4.8)         | 21.6 (7.2)      |
| Male, n (%)                                       | 8 (57.1)           | 7 (50.0)        |
| BMI in kg/m <sup>2</sup> , mean (SD)              | 24.2 (3.3)         | 22.9 (1.9)      |
| Pre-injury Tegner score, mean (SD)                | 7.8 (1.1)          | 7.3 (1.1)       |
| Non-contact trauma, n (%)                         | 11 (78.6)          | 13 (92.9)       |
| Time from injury to surgery in months, mean (SD)  | 4.3 (1.6)          | 4.1 (1.9)       |
| Meniscus injury, n (%)                            | 6 (42.9)           | 9 (64.3)        |
| Meniscus intervention, n (%)                      | 5 (35.7)           | 7 (50.0)        |
| Grade 3-4 chondral defect, n (%)                  | 1 (7.1)            | 2 (14.3)        |
| Lateral extra-articular tenodesis, n (%)          | 5 (35.7)           | 7 (50.0)        |
| Quadriceps strength at 60°/s in Nm/kg, mean (SD)  | 3.8 (1.4)          | 4.2 (1.1)       |
| Quadriceps strength at 180°/s in Nm/kg, mean (SD) | 3.2 (1.0)          | 3.3 (0.8)       |
| Quadriceps strength at 300°/s in Nm/kg, mean (SD) | 3.0 (1.0)          | 3.0 (0.8)       |
| Hamstring strength at 60°/s in Nm/kg, mean (SD)   | 2.6 (0.8)          | 3.2 (0.9)       |
| Hamstring strength at 180°/s in Nm/kg, mean (SD)  | 2.5 (0.8)          | 3.2 (1.0)       |
| Hamstring strength at 300°/s in Nm/kg, mean (SD)  | 2.2 (0.9)          | 2.6 (1.1)       |

BMI, body mass index; HLRT, heavy-load resistance training; kg/m<sup>2</sup>, kilograms per square meter; LL-BFRT, low-load blood flow restriction training; n, number of patients; Nm/kg, Newton-meters per kilogram; SD, standard deviation.

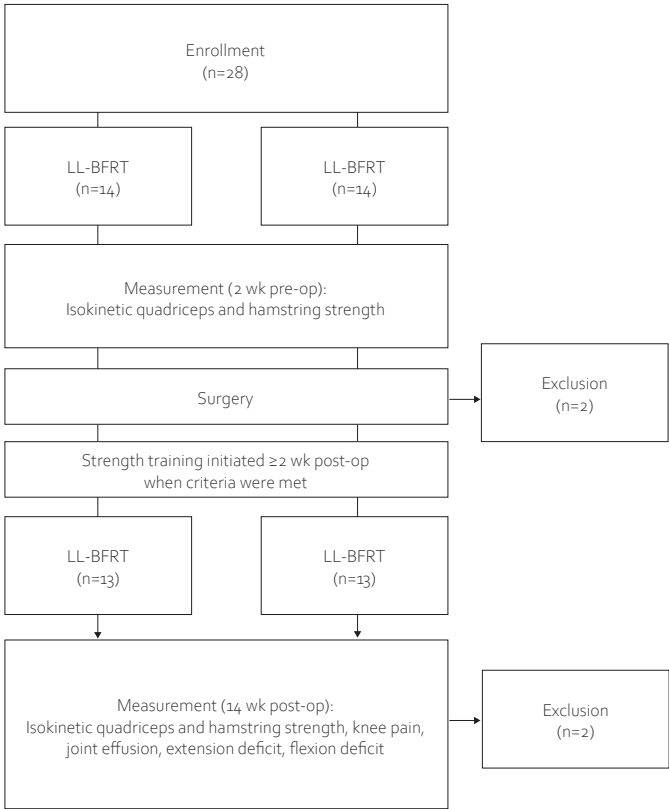


**Figure 1.** Flowchart of study.  
HLRT, heavy-load resistance training; LL-BFRT, low-load blood flow restriction training; n, number of patients; post-op, postoperatively; pre-op, preoperatively; wk, week(s).

### Primary outcome measurements

Table 2 summarizes isokinetic quadriceps and hamstring strength at 14 weeks postoperatively, assessed at different angular velocities. No statistically significant differences were found between groups for any muscle group or velocity. Independent samples t-test was used for all comparisons, and after applying the Benjamini-Hochberg correction for multiple testing, all results remained non-significant. Secondary outcome measurements

**Table 2.** Muscle strength measurements 14 weeks postoperatively.

|                                                   | LL-BFRT group<br>n=14 | HLRT group<br>n=14 | p-value |
|---------------------------------------------------|-----------------------|--------------------|---------|
| Quadriceps strength at 60°/s in Nm/kg, mean (SD)  | 2.7 (0.06)            | 3.1 (1.1)          | 0.738   |
| Quadriceps strength at 180°/s in Nm/kg, mean (SD) | 2.3 (0.6)             | 2.8 (1.0)          | 0.387   |
| Quadriceps strength at 300°/s in Nm/kg, mean (SD) | 2.2 (0.7)             | 2.8 (1.0)          | 0.387   |
| Hamstring strength at 60°/s in Nm/kg, mean (SD)   | 3.2 (0.7)             | 3.1 (1.0)          | 0.738   |
| Hamstring strength at 180°/s in Nm/kg, mean (SD)  | 3.2 (1.0)             | 2.9 (1.0)          | 0.738   |
| Hamstring strength at 300°/s in Nm/kg, mean (SD)  | 2.8 (0.7)             | 2.6 (1.2)          | 0.738   |

HLRT, heavy-load resistance training; LL-BFRT, low-load blood flow restriction training; n, number of patients ; Nm/kg, Newton-meters per kilogram; SD, standard deviation.

At final follow-up, 14 weeks postoperatively, knee pain was reported by two patients (14.3%) in the LL-BFRT group and five patients (35.7%) in the HLRT group ( $p=0.380$ ). Joint effusion was present in one patient (7.1%) in the LL-BFRT and five patients (35.7%) in the HLRT group ( $p=0.444$ ). At the final follow-up, one patient (7.1%) in the LL-BFRT group had a flexion deficit compared to four patients (28.6%) in the HLRT group ( $p=0.423$ ). None of the patients (0.0%) in the LL-BFRT group had an extension deficit, whereas two patients (14.3%) in the HLRT group had an extension deficit ( $p=0.478$ ). The exercise completion rates were 91.6% for the LL-BFRT and 94.9% for the HLRT group. Chi-square tests were used for all comparisons, and after applying the Benjamini-Hochberg correction for multiple testing, all results remained non-significant.

## Discussion

This study demonstrates that LL-BFRT in the early-stage rehabilitation following BPTB ACL reconstruction resulted in comparable quadriceps strength, hamstring strength, knee pain, joint effusion and range of motion compared to HLRT. These findings indicate that LL-BFRT may be an effective alternative to HLRT in the early-stage rehabilitation of BPTB ACL reconstructions.

One of the main priorities of rehabilitation after ACL reconstruction is optimal restoration of muscle strength while minimizing mechanical stress on the knee joint. The evidence regarding the effects of LL-BFRT following ACL reconstruction compared to HLRT remains limited (23,54). The present study found similar quadriceps and hamstring strength between LL-BFRT and HLRT. These findings contrast with findings from Hughes et al. and Vieira et al., showing increased quadriceps and hamstring strength after LL-BFRT compared to HLRT (23,54). The application of LL-BFRT in their study was similar to ours and in line with current recommendations, suggesting training durations of 6-12 weeks and the use of personalized cuff pressures (10). Additionally, the HLRT protocol was similar to our study. However, a key difference is that Vieira et al. implemented HLRT during the first

week following ACL reconstruction without assessing patients' eligibility before starting strength training (54). This raises the question whether patients in their study were able to tolerate and complete HLRT exercises in the early postoperative period. In contrast, both our study and that of Hughes et al. initiated HLRT two weeks postoperatively, after patients met the criteria to start with strength training (23). Criteria-based initiation of strength training led to a high percentage of patients successfully completing the strength training protocols. Hughes et al. observed that 91.2% of LL-BFRT and 87.5% of HLRT exercises were completed, leading to a significantly lower exercise volume in the HLRT group compared to the LL-BFRT group (23). In our study, the exercise completion rates were 91.6% and 94.9% for LL-BFRT and HLRT, respectively. Thus, we assume that differences in training tolerance and total exercise volume may explain the differences in results compared to our study.

In addition to restoration of muscle strength, it is important to address knee pain, decrease joint effusion and regain range of motion in the early-stage rehabilitation following ACL reconstruction. Moreover, the absence of knee pain, joint effusion and range of motion deficits is recommended before initiating mid-stage rehabilitation (3-5,41,53). The application of LL-BFRT has been suggested as an alternative to HLRT for the elderly and injured/postoperative patients, where HLRT may exacerbate knee pain (15,17,20-23,33). Previous studies have reported improved pain relief with LL-BFRT compared to HLRT following ACL reconstruction (20,22,23). Although not statistically significant, the present study observed fewer patients experiencing knee pain after LL-BFRT compared to HLRT. The dichotomous measurement used in this present study is less sensitive for detecting differences in pain compared to validated scoring systems such as the Knee Injury and Osteoarthritis Outcomes Scores used in previous studies (20,22,23). It is believed that pain relief with LL-BFRT is due to the combination of low external loads and its hypoalgesia effects compared to HLRT (15,28,29).

Reducing joint effusion is another essential aspect of rehabilitation, as joint effusion can limit full range of motion and negatively impact proprioception (25,42). In the present study, LL-BFRT was associated with fewer cases of joint effusion compared to HLRT, although this difference was not statistically significant. Hughes et al. demonstrated that LL-BFRT was beneficial in reducing joint effusion in early-stage ACL rehabilitation compared to HLRT (23). In their study, mid-patella knee joint circumference was used to assess joint effusion, a method that is more sensitive in detecting changes compared to the dichotomous measurement used in the present study. The beneficial effects of LL-BFRT on reduced joint effusion are likely due to its ability to optimize muscle strength while minimizing mechanical stress on the knee joint.

The recovery of range of motion is an important aspect of early-stage rehabilitation following ACL reconstruction. Full knee extension is essential to achieve normal gait

biomechanics (4,53). Furthermore, extension deficits may increase the risk of knee pain, cyclops lesions, and arthrofibrosis (9,18,38,45,47). In addition, sufficient knee flexion should be achieved to begin with cycling and running. The present study observed less extension and flexion deficits in the LL-BFRT group compared to the HLRT group. However, this difference did not reach statistical significance. Hughes et al. observed a beneficial effect of LL-BFRT on knee range of motion compared to HLRT following ACL reconstruction (23). The lower prevalence of knee pain and joint effusion with LL-BFRT may have contributed to fewer patients experiencing knee extension and flexion deficits compared with HLRT.

While this study found that LL-BFRT resulted in similar muscle strength as HLRT, safety considerations are essential when implementing this training modality. One patient in this study experienced fainting during the first LL-BFRT session. Although fainting during LL-BFRT is rare, with a reported incidence of less than 4%, it may occur due to a mismatch between cardiac output, vasomotor control, and local hyperemia mechanisms (1,8,19). However, in individuals without underlying medical conditions, fainting may also be triggered by stress or anxiety related to cuff tightness or pain. Pain during LL-BFRT may be due to cuff pressure and inflation time (43,50,56). This study followed evidence-based recommendations, using a cuff pressures of 80% of LOP with 120-180 of seconds deflation between sets (43). However, a recent study found that when using 80% of LOP, some patients require a reduction in cuff pressure due to pain (46). Additionally, a recent systematic review demonstrated that LL-BFRT with LOP of 40% resulted in similar strength improvements compared to LOP of 80% (7). Based on this evidence, we recommend using individualized LOP between 40% and 80% and starting BFRT at lower pressures to enhance familiarization and reduce potential side effects.

This study has several limitations. Firstly, blinding of patients and personnel could not be performed. This could affect the results, as patients may have experienced a novelty effect due to the nature of LL-BFRT. Secondly, total exercise volume in kilograms was not assessed, which may have introduced potential bias in the study's outcomes. Nevertheless, the training protocol and external load were well-defined, with a gradual increase in load throughout the intervention, aligning with standard rehabilitation practices. Thirdly, the relatively small study population and failure to reach the intended sample size may have reduced statistical power and increased the risk of type II error. Fourthly, the use of dichotomous outcome measurements for knee pain, joint effusion, and range of motion deficits may have limited the depth and quality of the analysis. However, these outcome measurements are commonly used to evaluate readiness for rehabilitation progression and are considered clinically relevant. Lastly, this study focused on the short-term effects of LL-BFRT, and further research is needed to evaluate its long-term impact.

In conclusion, the present study demonstrated that LL-BFRT in early-stage rehabilitation following BPTB ACL reconstruction resulted in similar quadriceps strength, hamstring

strength, knee pain, joint effusion and range of motion compared to HLRT. These findings suggest that LL-BFRT may be a safe alternative to HLRT for patients who may not tolerate HLRT or have contra-indications for HLRT.

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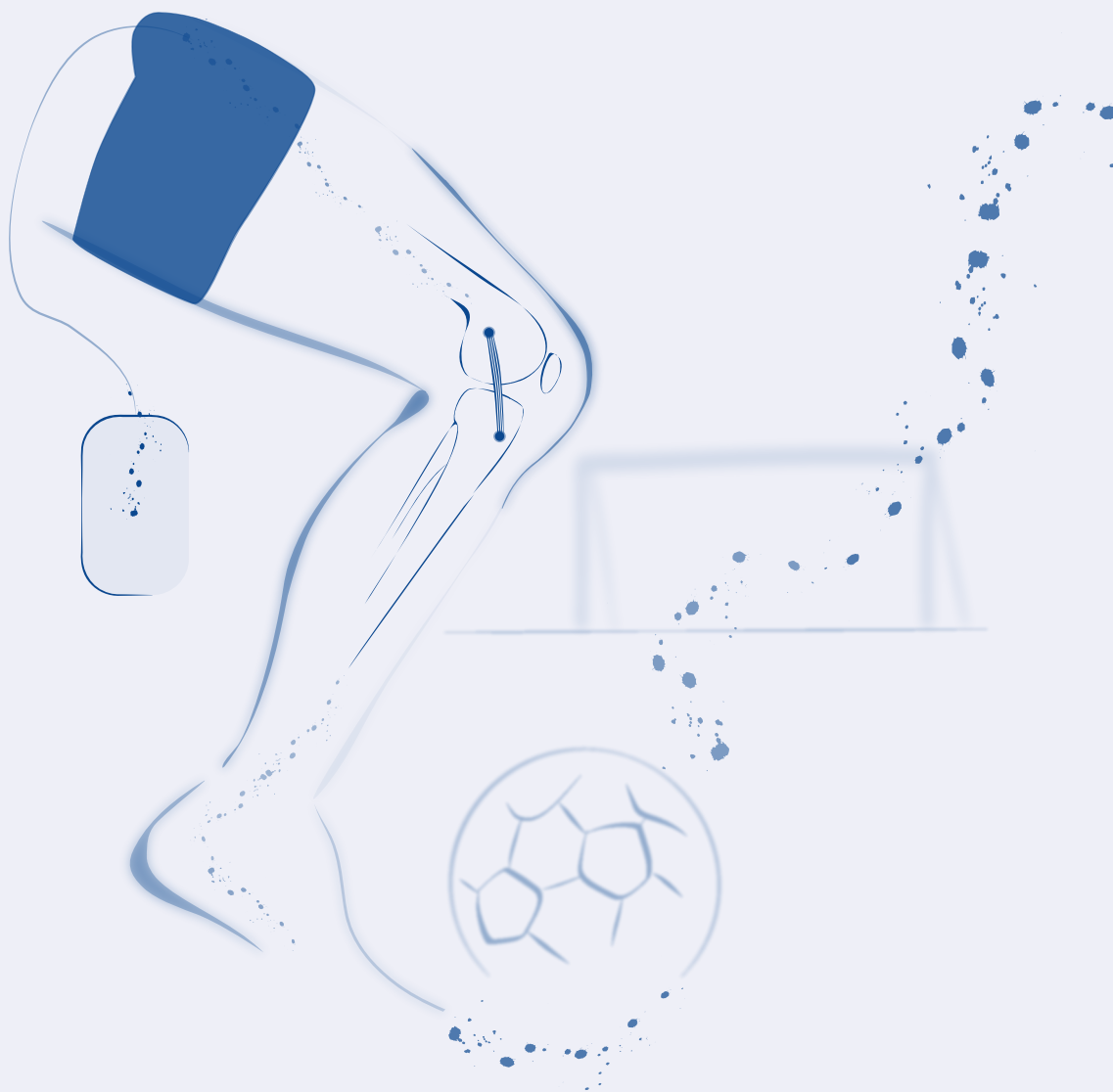
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# Chapter 6

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## **Qualitative evaluation of patient experiences with low-load blood flow restriction and heavy-load resistance training post-ACL reconstruction**

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## Abstract

**Background:** Low-load blood flow restriction training (LL-BFRT) has been suggested as an alternative to heavy-load resistance training (HLRT) following anterior cruciate ligament (ACL) reconstruction. While current research primarily focuses on the clinical outcomes of LL-BFRT and HLRT, patients' experiences with these rehabilitation methods remain unexplored. Such an exploration may provide insights that can contribute to more patient-centered rehabilitation approaches.

**Purpose:** This study aims to explore patients' experiences with strength rehabilitation using LL-BFRT or HLRT following ACL reconstruction. Study design: Qualitative Cohort study.

**Methods:** Patients who had undergone primary bone-patellar tendon-bone ACL reconstruction and completed an LL-BFRT or HLRT protocol within the prior six months were contacted to participate in semi-structured interviews. All interviews were audio-recorded, transcribed verbatim, and anonymized. An inductive thematic analysis was conducted to identify key themes and patterns.

**Results:** Ten participants were interviewed, with five in the LL-BFRT group and five in the HLRT group. The interviews were conducted, on average, four months after completion of the strength rehabilitation protocol. The inductive thematic analysis revealed four main themes: experiences with strength training, perceived benefits, challenges encountered, and impact on the recovery process. All participants experienced progression in muscle strength. Three participants in the LL-BFRT group reported thigh muscle pain, whereas four participants in the HLRT group noted knee pain during strength rehabilitation. Overall, participants had positive views on their recovery process, except for two participants in the HLRT group who reported negative effects on their recovery due to persistent knee pain.

**Conclusion:** The results of this study highlights patients' experiences with LL-BFRT and HLRT following ACL reconstruction. The findings indicate that LL-BFRT may be suitable in the early rehabilitation phase, as knee pain in the HLRT group may negatively affect the recovery process.

## Introduction

Rehabilitation following anterior cruciate ligament (ACL) reconstruction is crucial for restoring knee muscle strength and facilitating a successful return-to-sport (1-4). However, despite rehabilitation, muscle strength deficits following ACL reconstruction are common (5,6). This is concerning, as muscle strength deficits are associated with reduced patient-reported knee function and lower return-to-sport rates among both recreational and competitive athletes (6-10). Therefore, optimizing muscle strength recovery following ACL reconstruction is essential.

Heavy-load resistance training (HLRT), using external loads of more than 60% of one-repetition maximum (1RM), is currently recommended to improve muscle strength (11). However, there are concerns that HLRT following ACL reconstruction may have detrimental effects on knee pain (12). Therefore, low-load blood flow restriction training (LL-BFRT), using external loads between 20 and 40% of 1RM, has been suggested as an alternative to HLRT (10,12). During LL-BFRT, a pressurized cuff is applied to the proximal thigh that occludes venous outflow while partially restricting arterial inflow (13,14). The combination of venous occlusion and low-load (20-40% of one repetition maximum) resistance training during LL-BFRT is believed to induce muscle hypertrophy secondary to muscle tension and metabolic stress (15,16). Studies suggest that LL-BFRT can achieve muscle strength gains comparable to HLRT while exerting less mechanical stress on the knee joint (17-20). Additionally, LL-BFRT has demonstrated positive effects on functional outcomes in ACL-reconstructed patients and is increasingly applied in sport rehabilitation settings to support return-to-sport (18,20). While most existing studies have focused on clinical outcomes following LL-BFRT or HLRT, limited attention has been given to how athletes experience and perceive these rehabilitation methods in practice. Since successful rehabilitation depends not only on clinical efficacy but also on patient experience and adherence, a qualitative evaluation is essential to determine whether these rehabilitation methods effectively support recovery and return-to-sport participation. This study aims to explore patients' experiences with strength rehabilitation using LL-BFRT or HLRT following ACL reconstruction. These results will provide insights that can contribute to more patient-centered rehabilitation approaches and ultimately improve return-to-sport outcomes.

## Methods

### Design

This descriptive qualitative study using an inductive thematic analysis approach complies with the Declaration of Helsinki and was approved by the medical ethical committee. Furthermore, this study was performed in accordance with the Consolidated Criteria

for Reporting Qualitative Research (21). All patients provided informed consent before enrollment.

## Participants

Participants were recruited from a clinical trial examining low-load blood flow restriction (LL-BFRT) and heavy-load resistance training (HLRT) following bone-patellar tendon-bone (BPTB) ACL reconstruction. The participants were contacted if they were within six months post-strength rehabilitation. Patients not willing or able to participate were excluded.

Additionally, patients with a history of venous thromboembolism, sickle cell anemia, hypertension or other relevant cardiovascular conditions were excluded from the study due to limited evidence regarding the safety of LL-BFRT in this population (22). The recruitment process and inclusion of participants are illustrated in Figure 1.

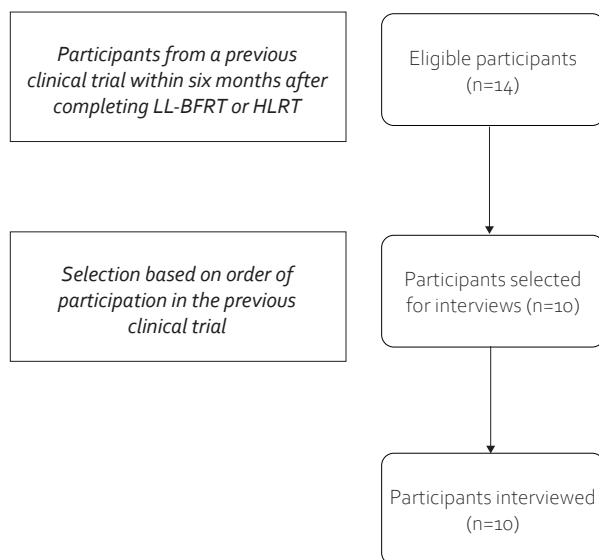


**Figure 1.** Flowchart of participant recruitment.

## Surgical procedure

All participants underwent ACL reconstruction using an autologous BPTB graft. The anteromedial portal was used to place the femoral tunnel in the isometric anteromedial bundle position. The tibial tunnel was placed in the center of the native ACL footprint. This approach aligns with current concepts for achieving an anatomic tunnel placement and optimal ACL reconstruction (23). Titanium interference screws (Zimmer Biomet, Indiana, USA) were used for femoral and tibial graft fixation. Additionally, a modified Lemaire lateral extra-articular tenodesis (LET) was performed in patients with preoperative high-

grade pivot shift or hyperlaxity (24). The surgical procedures were performed by high-volume ACL surgeons.

## Strength rehabilitation protocol

All participants followed the same standardized rehabilitation program under the guidance of physiotherapists specialized in ACL rehabilitation. The only difference between groups was the type of strength intervention (LL-BFRT or HLRT), which was implemented between two and 14 weeks postoperatively. Two weeks after surgery, patients started a biweekly strength training protocol for 12 weeks if they had a knee range of motion of 0-90°, had no or minimal effusion during activity (defined as trace or 1+ based on the stroke test) and were able to perform repeated straight leg raises (12,25). The strength training included leg press, leg extension, deadlift and squat exercises, with 30 seconds of rest between sets and 120 to 180 seconds of rest between exercises. Blood flow restriction in the LL-BFRT group was achieved using an automatic tourniquet system (PTS; MAD-UP, Angers, France) designed to automatically calculate limb occlusion pressure. Limb occlusion pressure was defined as the minimum pressure required for arterial blood flow occlusion. Limb occlusion pressure of 80% was applied during each exercise and was determined in the position that the exercise was performed in. The cuff was inflated during each exercise and deflated during the 120 to 180 seconds of rest between exercises. Patients in the LL-BFRT group performed four sets per exercise, consisting of 30, 15, 15, and 15 repetitions, with 30 seconds of rest between sets while the cuff remained inflated. Each exercise was performed at 30% of 1RM (12-14). Patients in the HLRT group performed three sets (10, 10, 10 repetitions) of each exercise at 70% of 1RM (12-14). The 10RM strength was measured and used to predict 1RM strength (26). The external training load was increased by 10% if patients completed all repetitions on two subsequent strength training sessions (11).

## Data collection

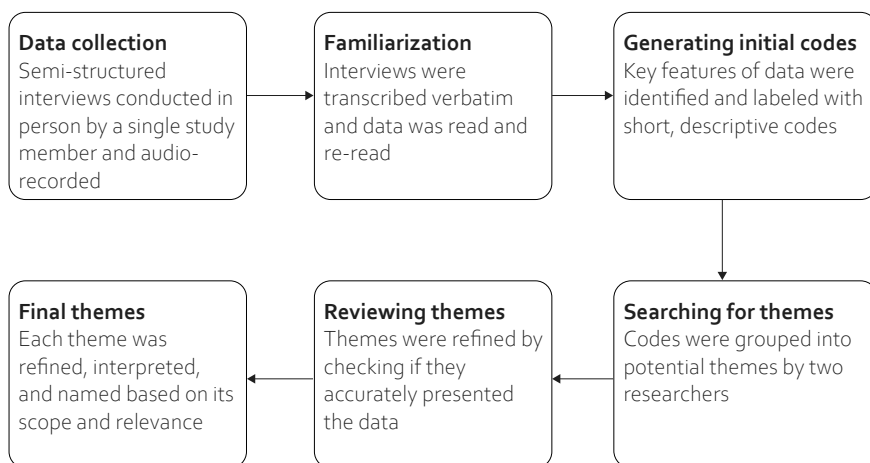
Semi-structured interviews were conducted between May and June 2023 using an interview guide. The interview guide was based on a literature review and included topics and questions related to patients' experiences with strength training (LL-BFRT and HLRT) (Supplemental File 1) (18,27-30). A single study member conducted all in-person interviews, which were audio-recorded, transcribed verbatim and anonymized. Data saturation was reached when no new themes, insights, or dimensions emerged from the interviews (31). The number of participants depended on the time to saturation within every group. It was estimated that four participants per group would be sufficient to reach saturation. In total, ten participants were invited to participate in the study.

**Supplemental file 1.** Interview guide.

1. Can you describe your experience with the strength rehabilitation program?
2. How would you rate your satisfaction with the strength rehabilitation program and which factors influenced your satisfaction?
3. What aspects of the strength rehabilitation program did you find beneficial? Why?
4. What aspects of the program did you find challenging? Why?
5. Did you notice any improvements during strength rehabilitation? If so, which ones?
6. Did you experience any discomfort or adverse events during strength rehabilitation? If so, can you describe them?
7. How would you describe your adherence to the strength rehabilitation program? What factors influenced your adherence?
8. How would you describe your overall recovery?
9. In what ways do you feel the strength rehabilitation contributed to your overall recovery?
10. How would you describe your overall recovery in terms of walking without crutches and returning to running or other activities? When did you achieve these milestones?
11. Which aspects have influenced your overall recovery process?
12. Were there any aspects of the rehabilitation that exceeded or fell short of your expectations?
13. Is there anything else you would like to share about your rehabilitation experience?

**Data analysis**

Demographic data, including age, gender, pre-injury Tegner score, trauma mechanisms, and concomitant treatments (such as partial meniscectomy and LET procedure), as well as patient satisfaction ratings (0-10, 10 very satisfied) were collected. An inductive thematic analysis was used to analyze the transcripts according to the six phases described by Braun and Clarke.<sup>32</sup> One researcher read and coded the transcripts. After completion of the coding process, two researchers discussed and analyzed the codes to identify themes and subthemes of the study. These themes were then listed to ensure adequate representation of the data. An overview of the data collection and analysis process is presented in Figure 2.

**Figure 2.** Data collection and analysis process.

## Results

A total of ten participants were included in the study, with five in the LL-BFRT group and five in the HLRT group (Table 1). Data saturation was reached after four participants per group, and this was confirmed after the fifth interview, as no new themes or dimensions emerged. The interviews were conducted, on average, four months after completing the strength rehabilitation protocol. Among the participants, six were male. The median age in the LL-BFRT group was 24.6 years (range 23-27), while in the HLRT group, it was 22.8 years (range 19-33). The median patient satisfaction rates were 8.5 (range 7.5-9.0) for the LL-BFRT group and 7.9 (range 7.0-9.0) for the HLRT group, respectively. In total four themes were identified: 1. experiences with strength training, 2. perceived benefits, 3. challenges encountered and 4. impact on the recovery process.

**Table 1.** An overview of participants.

| Nr            | Age | Gender | Pre-injury<br>Tegner<br>score | Trauma<br>mechanism | Partial<br>meniscec-<br>tomy | LET | Satisfaction<br>rate | Period after<br>strength<br>rehabilitation |
|---------------|-----|--------|-------------------------------|---------------------|------------------------------|-----|----------------------|--------------------------------------------|
| LL-BFRT<br>01 | 27  | M      | 7                             | Noncontact          | Yes                          | No  | 9.0                  | 3 months                                   |
| LL-BFRT<br>02 | 25  | F      | 7                             | Noncontact          | No                           | No  | 7.5                  | 5 months                                   |
| LL-BFRT<br>03 | 24  | F      | 9                             | Noncontact          | No                           | Yes | 9.0                  | 4 months                                   |
| LL-BFRT<br>04 | 23  | M      | 7                             | Noncontact          | No                           | No  | 8.0                  | 5 months                                   |
| LL-BFRT<br>05 | 24  | M      | 9                             | Contact             | No                           | Yes | 9.0                  | 4 months                                   |
| HLRT<br>01    | 19  | M      | 7                             | Contact             | No                           | No  | 8.0                  | 4 months                                   |
| HLRT<br>02    | 20  | F      | 7                             | Noncontact          | Yes                          | No  | 7.5                  | 3 months                                   |
| HLRT<br>03    | 20  | M      | 7                             | Noncontact          | No                           | No  | 7.0                  | 5 months                                   |
| HLRT<br>04    | 22  | M      | 9                             | Noncontact          | Yes                          | Yes | 8.0                  | 4 months                                   |
| HLRT<br>05    | 33  | F      | 7                             | Noncontact          | No                           | Yes | 9.0                  | 4 months                                   |

LL-BFRT, low-load blood flow restriction training; HLRT, heavy-load resistance training; M, Male; F, Female; LET, lateral extra-articular tenodesis.

### 1. Experiences with strength training

The participants were satisfied with both strength protocols. They reported that physiotherapist-patient relationship, quality of physiotherapy care, expectations and results

influenced their experience with strength training. *"The experience of the physiotherapists and the personalized attention had a positive effect on my strength rehabilitation process"* (Participant 2, HLRT group). The strength rehabilitation was acknowledged as challenging, yet all participants recommended the strength rehabilitation protocol to gain muscle strength. *"The strength rehabilitation was intense, but the results exceeded my expectations"* (Participant 1, LL-BFRT group).

## 2. Perceived benefits

All participants recognized a progression in muscle strength, stability and ability to undertake activities. The increase in muscle strength motivated the participants to continue with strength training. *"I am pleased with the progress I have made in building muscle strength. I have more confidence in my knee"* (Participant 4, HLRT group). In addition, with the exception of two participants in the HLRT group, all participants experienced a decrease in pain and increase in knee confidence during strength rehabilitation. *"I had less knee pain, and I was more confident than at the start of my rehabilitation"* (Participant 3, LL-BFRT group).

## 3. Challenges encountered

All participants stated that the strength rehabilitation program was challenging. Three participants in the LL-BFRT group noted thigh muscle pain during strength rehabilitation. Furthermore, one participant in the LL-BFRT group fainted during the first training session. *"The cuff pressure on my thigh was intense and I fainted during the first training session"* (Participant 2, LL-BFRT group). In the HLRT group, two participants reported knee pain during strength rehabilitation, with two other participants reporting knee pain during and after strength rehabilitation. *"I noticed significant knee pain during and following my strength training program"* (Participant 2, HLRT group).

## 4. Impact on recovery process

All participants experienced positive effects on their recovery process, except for two participants in the HLRT group who experienced negative effects with a delayed recovery process. Participants who reported positive effects on their recovery process stated to be able to bear weight without crutches within six weeks, run without pain or swelling within 14 weeks and return to on field rehabilitation within 20 weeks post-surgery. *"I felt stronger and more confident thanks to my muscle strength gains. I started on field rehabilitation four months after ACL reconstruction"* (Participant 4, LL-BFRT group). Participants who reported negative effects on their recovery process stated that they were able to bear weight without crutches 10-12 weeks after surgery and were not able to run without pain. *"Knee pain prolonged my rehabilitation and restricted the ability to perform kneeling activities"* (Participant 3, HLRT group). The positive effects on the recovery process were the result

of pain-free return to activities, unrestricted range of motion, improved muscle strength, confidence in the knee and improved physical performance. The negative effects on the recovery process were due to knee pain during and after activities.

## Discussion

This qualitative study showed high patient satisfaction with low-load blood flow restriction training (LL-BFRT) and heavy-load resistance training (HLRT) following anterior cruciate ligament (ACL) reconstruction. In addition, all participants reported improvements in muscle strength. However, differences were noted in the challenges faced and the overall impact on recovery.

Patient satisfaction was high for both LL-BFRT and HLRT, with all participants completing and recommending these rehabilitation protocols. Participants emphasized the importance of the physiotherapist-patient relationship, the quality of physiotherapy care, and the alignment of their expectations with their outcomes. These factors influenced their satisfaction with both LL-BFRT and HLRT protocols.

All participants experienced improvements in muscle strength, which is consistent with the results of previous studies examining the effectiveness of these rehabilitation methods after ACL reconstruction (33,34). In addition to the literature, the present study found that some participants experienced an improvement in knee confidence with both LL-BFRT and HLRT. This finding is significant because knee confidence can influence patient behavior, impacting rehabilitation outcomes such as adherence to physiotherapy sessions and training effort (35).

Both strength rehabilitation protocols were perceived as challenging by all participants. However, side effects varied between the two groups. In the LL-BFRT group, one participant reported a temporary loss of consciousness during the first session, and three participants experienced thigh muscle pain during training. In the HLRT group, two participants reported knee pain during training, while two other participants noted knee pain both during and after training. Fainting during LL-BFRT is rare, with reported incidence in the literature being less than 4% (36). Hogan et al. suggested that fainting could result from a mismatch between cardiac output, sympathetic control of the vasomotor system, and local mechanisms of hyperemia (37). LL-BFRT may affect cardiac output by reducing the cardiac preload due to venous occlusion generated by the application of a pressurized cuff on the thigh (17). If an individual's compensation mechanisms are insufficient, these changes could lead to fainting. However, in individuals without underlying medical conditions, fainting could also be triggered by stress or anxiety from cuff tightness or pain.

The authors speculate that stress or anxiety could have contributed to the young female participant's fainting in this study. Additionally, thigh muscle discomfort during LL-BFRT might be influenced by factors such as cuff pressure and inflation time (38-40). Participants in this study followed an LL-BFRT protocol based on current evidence recommending a cuff pressure between 40 and 80% of limb occlusion pressure (LOP) and intermittent blood flow restriction with 30 seconds of rest between sets (38). All participants of the present study following the LL-BFRT protocol had their cuff pressure set at 80% of LOP. A recent study using the same LOP setting showed that in 4% of training sessions a decrease in pressure was needed due to pain (41). Additionally, a recent systematic review demonstrated significant results on muscle strength when LL-BFRT was performed with LOP between 40 and 80% (42). Based on this evidence, the authors recommend using an individualized LOP between 40 and 80%. In contrast to LL-BFRT, knee pain was commonly reported in the HLRT group. Two participants experienced knee pain during HLRT, while two other participants noted knee pain both during and after training. These findings are consistent with previous studies (12,33,43). This may be the result of higher mechanical stress to the knee joint with HLRT by using higher external loads compared to LL-BFRT. Furthermore, the use of LL-BFRT may enhance the analgesic effects of exercise-induced hypoalgesia (44-46).

Rehabilitation is vital for ensuring a successful recovery and follows a criteria-based progression that begins with controlling symptoms such as knee pain and effusion (1-4). Once these are managed, the focus shifts to rebuilding muscle strength and neuromuscular control, ultimately progressing to functional and sport-specific training (1-4). However, pain and effusion management remain essential throughout each phase of the rehabilitation (1-5). Failure to maintain control over these symptoms can negatively impact recovery, potentially hindering an athlete's readiness and ability to return-to-sport at the desired performance level (47-51). All participants who adhered to the LL-BFRT protocol reported a beneficial impact on their recovery process. In contrast, two participants in the HLRT group experienced delayed recovery due to knee pain. As LL-BFRT promotes muscle strength while minimizing mechanical stress on the knee joint, this method may positively influence pain management, overall recovery, and ultimately enhance return-to-sport outcomes compared to HLRT. Nevertheless, to date there is no data available on the effects of LL-BFRT on functional performance assessments and return-to-sport rates in comparison to HLRT.

The present study has several limitations. First, the small sample size may limit the generalizability of the findings of the present qualitative study. However, the study reached data saturation with consistent and recurring themes in athletes' experiences with LL-BFRT and HLRT, supporting the strength of the current findings. Secondly, the interviews were conducted, on average, four months after completion of the strength rehabilitation protocol with the potential of recall bias. Given that all participants received a bone-patellar

tendon-bone (BPTB) graft for ACL reconstruction, the findings may not fully translate to populations treated with other graft types. This should be considered when interpreting the study's outcomes. Finally, factors like graft morbidity and psychological factors such as beliefs (e.g. placebo-effect), stress and coping mechanisms may affect knee pain and were not assessed in the present study. However, this is the first study assessing patients' experience with LL-BFRT and HLRT allowing participants to express their experiences in greater depth and detail.

## Conclusion

The results of the present study provide valuable insights to enhance patient-centered strength rehabilitation following ACL reconstruction. Findings indicate that LL-BFRT may be more suitable in the early rehabilitation phase, as knee pain in the HLRT group may negatively affect the recovery process. However, further studies are needed to evaluate the role of LL-BFRT and HLRT on functional performance and safe return to sport after ACL reconstruction.

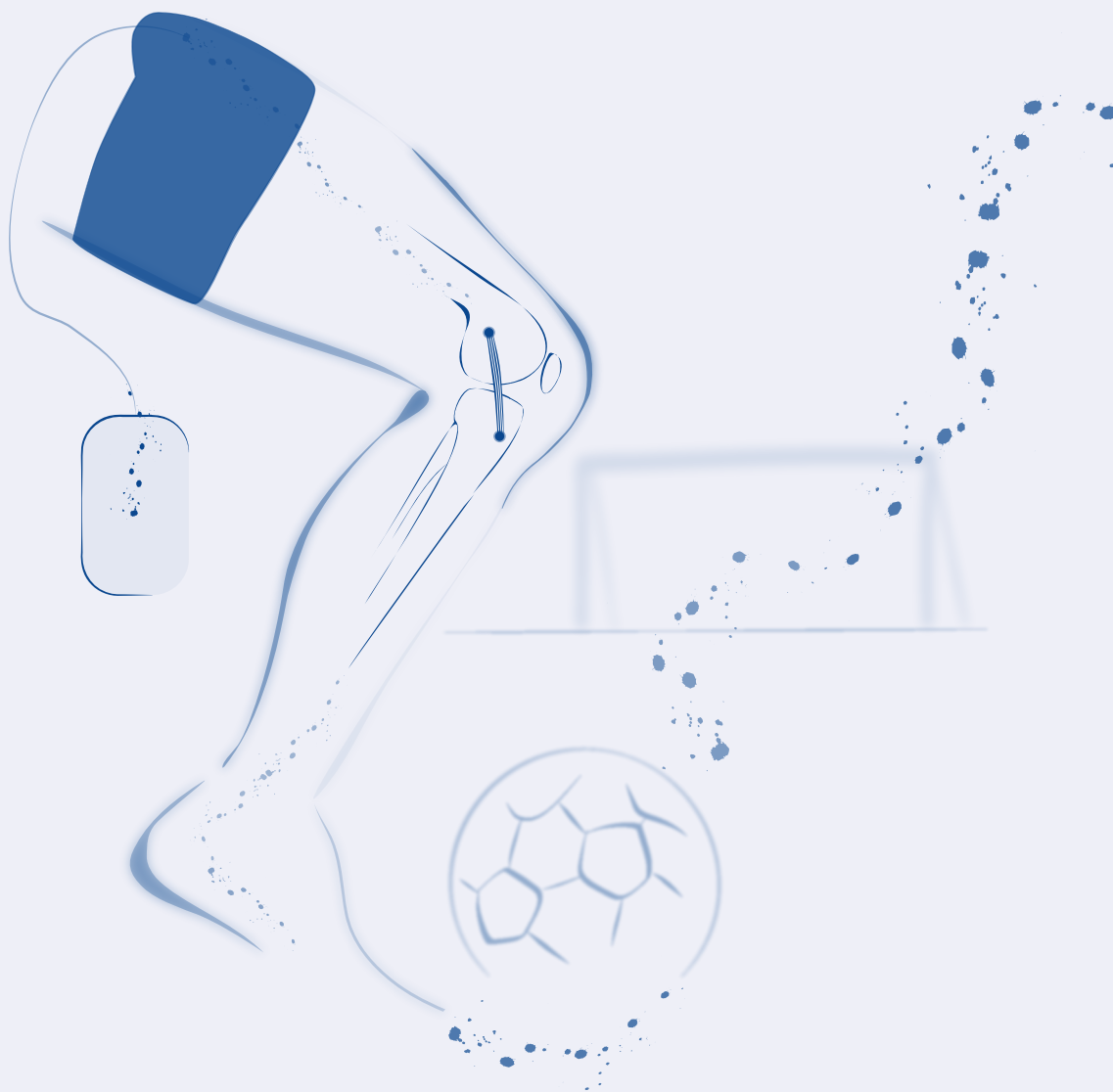
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# Chapter 7

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**General discussion**

## General discussion

This thesis aimed to improve outcomes following anterior cruciate ligament (ACL) reconstruction by examining current trends in surgical techniques and return to sport (RTS) criteria in the Netherlands. It also aimed to identify predictors of patient satisfaction, and to explore the role of low-load blood flow restriction training (LL-BFRT) in postoperative rehabilitation. This chapter synthesizes the key findings from previous chapters, discusses the findings, and their implications for clinical practice and future research directions.

### Part I ACL reconstruction in the Netherlands

The first part of this thesis investigated surgeons' preferences in the Netherlands regarding surgical techniques and RTS criteria. Findings from **Chapter 2** revealed that the majority of surgeons favor hamstring tendon (HT) autografts for primary ACL reconstruction and predominantly use the anteromedial and outside-in techniques for femoral tunnel placement. Additionally, surgeons emphasized the importance of both time- and testing-based criteria in determining RTS readiness.

HT autografts are widely used due to their lower donor-site morbidity, smaller incisions, and reduced risk of anterior knee pain compared to bone-patellar tendon-bone (BPTB) autografts (1-5). However, BPTB autografts are favored for their bone-to-bone healing, enabling faster graft incorporation and stronger fixation than HT autografts (6). Their consistent graft diameter (>9 mm) further enhances mechanical stability. Studies have consistently shown low failure rates with BPTB autograft, whereas research on HT autograft failure rates remains inconsistent (7-9). As a result, BPTB autografts are often preferred in young, high-level athletes who are at greater risk of ACL re-injury (9-11). In recent years, quadriceps tendon (QT) autografts have gained popularity due to their reduced risk of anterior knee pain compared to BPTB autografts, while demonstrating comparable ACL re-injury rates (12, 13). As more evidence supports their biomechanical strength and clinical benefits, the adoption of QT autografts is expected to rise. On the other hand, allografts, despite eliminating donor-site morbidity, are associated with higher infection rates and a threefold increase in ACL re-injury risk compared to autografts (14). As a result, their use in primary ACL reconstruction remains limited.

The findings in **Chapter 2**, on techniques for femoral tunnel placement align with current literature, showing that the anteromedial and outside-in techniques are the most commonly used methods (15-17). As understanding of ACL anatomy and biomechanics has improved, surgical preferences have shifted away from the transtibial technique toward these methods, aiming for more anatomical tunnel placement and improved joint stability (15-19). However, this thesis did not investigate the optimal target point for femoral tunnel placement. Literature suggests that placing the femoral tunnel at the center of the anteromedial bundle of the native ACL enhances knee stability and reduces

the risk of graft failure (20, 21). To aid in accurate placement, both the ruler method and bony landmarks, such as the lateral intercondylar ridge, the lateral bifurcate ridge, the proximal point, and the posterior point have been described (22). Despite these anatomical references, a study involving high-volume surgeons, defined as those performing at least 40 ACL reconstructions per year, reported a 20% mismatch between intended and actual femoral tunnel placement (23). This is concerning, as incorrect femoral tunnel placement accounts for up to 80% of technical errors and increases the risk of ACL graft failure (24, 25). To enhance accuracy, technology-assisted ACL reconstruction, including computer-assisted navigation, robotic systems, and 3D printing, is being explored. While these tools demonstrate potential for improving surgical precision, long-term studies are required to confirm their effectiveness in reducing graft failure rates and improving patient-reported outcomes (26-31). Although this thesis did not assess surgeon preferences regarding lateral extra-articular procedures (LEAPs), their role is increasingly recognized. LEAPs have been shown to improve rotational stability and reduce the risk of graft failure (32-34). Combining LEAPs with HT autografts in high-risk populations (e.g., young athletes engaged in pivoting sports or individuals with generalized ligamentous laxity) reduces the risk of re-injury by two- to fivefold (32-37). However, limited evidence exists to confirm whether these benefits apply to other commonly used grafts, such as BPTB or QT autografts (38, 39). Additionally, concerns remain regarding potential complications, including tunnel convergence and overconstraint (40-42). Further research is needed to identify which patients benefit most from LEAPs (43, 44). Determining readiness for RTS following ACL reconstruction remains a major clinical challenge. **Chapter 2** found that most surgeons recommend RTS no earlier than nine months following ACL reconstruction. Furthermore, surgeons highlighted the importance of supplementing time-based criterion with testing-based criteria, such as clinical examination, patient-reported outcome measurements, and functional performance tests, to guide whether an athlete is ready to RTS. This aligns with existing literature, which indicates that postoperative time alone is insufficient for ensuring safe and successful RTS. Research has demonstrated that athletes meeting RTS criteria before RTS are associated with four- to sixfold reduction in ACL re-injury risk (45, 46). In the literature, however, various RTS criteria are described, with passing percentages ranging between 10% and 70% (45-49). The highest passing rates have been observed in professional athletes, suggesting that baseline physical fitness, motivation, and access to rehabilitation resources may influence RTS success (45). Additionally, the more tests included in the RTS criteria, the lower the likelihood of passing (48). Overall, RTS criteria should include muscle strength, jump-landing performance, movement quality, and psychological readiness (45-51). In clinical practice, however, a study in the Netherlands demonstrated that fewer than 50% of athletes were cleared to RTS by their physiotherapists without undergoing RTS testing (52). This is concerning, as many athletes RTS without appropriate testing, which may increase the risk of ACL re-injury. Further studies are needed to investigate the

reasons behind the omission of RTS testing to enhance its application in clinical practice. Furthermore, given the distinct demands of different sports and activity levels, research should focus on developing individualized sport-specific RTS criteria to ensure a safe RTS.

## Part II Predictors of ACL reconstruction outcome

Most studies on ACL reconstruction primarily focus on outcomes such as RTS rates, re-injury risks, and patient-reported knee function. However, patient satisfaction, though less frequently evaluated, is a crucial outcome, as it reflects the extent to which the surgical outcome aligns with the patient's expectations and perceived value. The second part of this thesis investigated the influence of preoperative, operative, and postoperative factors on patient satisfaction following primary HT ACL reconstruction. **Chapter 3** demonstrated that neither patient characteristics nor surgical factors were predictive of patient satisfaction. In contrast, postoperative factors such as rehabilitation duration, RTS timing, and occurrence of re-injury had a significant impact on patient satisfaction. Furthermore, patient satisfaction was closely associated with return to pre-injury levels of sport participation and higher patient-reported knee function.

**Chapter 3** showed that preoperative factors such as age, gender, pre-injury activity level, body mass index, and mechanism of injury, do not influence patient satisfaction following ACL reconstruction. These findings complement existing literature, which has found no association between these variables and patient-reported knee function (53-58). Nevertheless, emerging evidence suggests that bony morphology, such as posterior tibial slope and intercondylar notch width, may influence ACL re-injury rates and patient-reported knee function (59-61). Despite their potential relevance, these anatomical factors were not evaluated in this study as predictors of patient satisfaction. Furthermore, **Chapter 3** found no association between patient satisfaction and operative variables, such as graft diameter and the presence or treatment of concomitant meniscal or cartilage injuries. In this study, all patients underwent ACL reconstruction using a triple-strand semitendinosus and double-strand gracilis autograft, with an average graft diameter of nine millimeters in both the satisfied and dissatisfied groups. Current literature presents inconsistent findings regarding the impact of HT graft diameter on re-injury rates and patient-reported outcomes (62-66). These inconsistencies highlight the need to consider additional surgical factors, such as tunnel placement, when evaluating ACL reconstruction success. Additionally, no distinction was made regarding the type of treatment for concomitant injuries, which is relevant since research suggests it may influence patient-reported outcomes. For instance, microfracture of focal grade 3-4 cartilage lesions performed during ACL reconstruction has been associated with inferior patient-reported knee function compared to debridement or no treatment (67). Furthermore, partial meniscectomy is associated with reduced knee function and stability compared to meniscal repair (68, 69). Patients undergoing partial meniscectomy also show a higher rate of chondral degeneration compared to those who

receive meniscal repair (70, 71). These findings emphasize the importance of meniscal preservation, reinforcing the approach of saving the meniscus whenever possible during primary ACL reconstruction, to optimize patient-reported outcomes.

Following ACL reconstruction, **Chapter 3** observed that a minimum of nine months of supervised rehabilitation, RTS clearance after nine months, and the absence of ACL re-injury were all positively associated with patient satisfaction. The nine-month timeline is often regarded in the literature as the minimum duration required to allow for adequate biological and neuromuscular recovery to ensure safe RTS (50, 72, 73). Biological recovery, known as the remodeling process of the ACL graft, follows three distinct phases: an early necrosis phase that may last up to four weeks, a proliferative phase lasting four to twelve weeks, and a final ligamentization phase lasting 12 weeks up to one year (74-76). A study reported that over 90% of HT autografts demonstrated good to excellent MRI signal intensity by nine months postoperatively, supporting the notion that RTS at this time may be biologically safe (77). Additionally, studies have reported improved graft remodeling with BPTB and QT autografts compared to HT autografts (78, 79). However, a biologically healed graft does not necessarily translate to neuromuscular readiness. Growing evidence highlights that neuromuscular recovery, including muscle strength and movement control, is critical in reducing the risk of ACL re-injury (45, 46). Current guidelines generally recommend at least nine months of supervised rehabilitation, not just for biological recovery of the ACL graft, but also to ensure sufficient neuromuscular control and safe RTS (50, 72, 73). However, **Chapter 3** also revealed that some patients who underwent rehabilitation for less than nine months or RTS before this timeframe reported high levels of satisfaction with their outcome following ACL reconstruction. This suggests that factors beyond the nine-month timeline influence both recovery and patient satisfaction. A recent study demonstrated that athletes who adhered to a criteria-based, sport-specific rehabilitation protocol and met established RTS criteria did not exhibit an increased risk of ACL re-injury, even if they RTS before nine months (80). While time is often used to recommend safe RTS, growing evidence indicates that how an athlete returns may be more critical than when they return (80-82). For this reason, not only the duration of rehabilitation but also its quality and an athlete's readiness for RTS should be considered when assessing patient satisfaction following ACL reconstruction.

**Chapter 3** further demonstrated that patient satisfaction is associated with both RTS at the pre-injury level and patient-reported knee function. These outcomes are particularly important, as studies show that approximately 85% of patients expect to return to their pre-injury level of sport, and nearly all anticipate experiencing no or minimal knee-related symptoms during physical activity (83, 84). However, these expectations do not always align with reality. Evidence indicates that only 65% of individuals successfully return to their pre-injury level of sport, and approximately 15% continue to experience knee-related symptoms following ACL reconstruction (85-88). Failure to meet preoperative expectations

is strongly linked to patient dissatisfaction, highlighting the need for data-driven decision-making (84, 89). Predictive models that incorporate patient characteristics, surgical factors, and recovery variables can provide accurate forecasts on RTS likelihood, ACL re-injury risk, and patient-reported outcomes. These models can assist both clinicians and patients in assessing the potential benefits and risks of ACL reconstruction, ensuring that treatment decisions are based by personalized data rather than assumptions. By integrating predictive models into preoperative counseling and treatment planning, healthcare professionals can help patients establish realistic expectations, make informed surgical decisions, and tailor rehabilitation strategies. Aligning expectations with evidence-based predictions reduces uncertainty, enhances shared-decision making, and ultimately contributes to improved patient satisfaction.

### Part III Low-load BFR training post-ACL surgery

One of the primary goals of rehabilitation following ACL reconstruction is to restore muscle strength while minimizing mechanical stress on the knee joint. The final part of this thesis explored the role of low-load blood flow restriction training (LL-BFRT) in the early phases of ACL rehabilitation. Findings demonstrate that LL-BFRT is an effective strategy for enhancing muscle strength while limiting joint loading, making it a valuable addition to conventional rehabilitation protocols during periods when heavy-load resistance training (HLRT) may not be feasible or safe.

The optimal strength rehabilitation method following ACL reconstruction remains a topic of debate. HLRT, which involves external loads greater than 60% of one-repetition maximum (1RM), is currently the gold standard for promoting muscle strength in healthy individuals (90). However, concerns have been raised that HLRT following ACL reconstruction may place excessive stress on the knee joint and may negatively affect ACL graft healing and knee pain (91-96). Alternatively, low-load resistance training (LLRT), involving external loads of less than 40% of 1RM, has been found to be less effective than HLRT in optimizing muscle strength (97, 98). These challenges have prompted the consideration of LL-BFRT as a potential alternative for strength rehabilitation following ACL reconstruction. Unlike LLRT, LL-BFRT includes arterial blood flow restriction during LLRT, which enhances its effectiveness.

The literature review in **Chapter 4**, which includes six randomized controlled trials, showed that LL-BFRT may offer advantages over LLRT in terms of quadriceps strength, quadriceps mass, and knee pain. Additionally, LL-BFRT demonstrated similar effects on quadriceps strength and mass as HLRT, while also contributing to a reduction in knee pain. However, a major limitation of the current literature is the variability in LL-BFRT protocols, including differences in cuff width, cuff pressure, and external training load. Current research on LL-BFRT recommends using wide cuffs (>10 cm), setting cuff pressure at 80% of limb occlusion pressure (LOP), and adhering to external loads between 20% and 40% of 1RM to optimize

training outcomes (99-103). Additionally, all studies included in the review focused on patients who underwent ACL reconstruction with an HT autograft, thereby limiting the generalizability of findings to other graft types. This limitation is particularly significant, as quadriceps strength deficits are more common following ACL reconstruction with a BPTB or QT autograft compared to an HT autograft (104-107).

**Chapter 5** demonstrates that LL-BFRT following ACL reconstruction with a BPTB autograft results in comparable quadriceps and hamstring strength relative to HLRT. However, the mechanisms by which these training methods promote muscle strength differ significantly. LL-BFRT enhances muscle strength through a combination of metabolic stress induced by venous occlusion and mechanical tension generated by low external loads during resistance training (108-110). In contrast, HLRT primarily relies on high mechanical tension induced by resistance training with heavy external loads to stimulate muscle strength (90). At the cellular level, studies show that LL-BFRT leads to the accumulation of metabolites such as lactate and hydrogen ions, which play a role in stimulating muscle strength, similar to HLRT (109, 110). Additionally, LL-BFRT has been shown to recruit type II fast-twitch muscle fibers at lower external loads, whereas these fibers are typically activated during HLRT (111-113). These findings support the use of LL-BFRT as a viable alternative for achieving neuromuscular adaptations. Since strength rehabilitation plays a crucial role in ACL recovery, it is essential to introduce strength training based on clear, evidence-based criteria to ensure both efficacy and safety (51, 114, 115). Common criteria for initiating strength training include the absence of significant joint effusion, full knee extension, and at least 90 degrees of knee flexion. Additionally, quadriceps activation must be sufficient to support controlled movements without compensatory strategies. **Chapter 5** demonstrated that when strength training is initiated two weeks post-surgery, based on these criteria, a high percentage of patients can successfully complete the LL-BFRT and HLRT protocols. Exercise completion rates were 91.6% for LL-BFRT and 94.9% for HLRT, respectively. While these results highlight the effectiveness of early, criteria-based strength training, safety considerations remain paramount. A key challenge in strength rehabilitation following ACL reconstruction is achieving an optimal balance between applying sufficient external training load to stimulate muscle strengthening and protecting the healing ACL graft and knee joint (51, 114, 115). The ACL graft is most vulnerable to mechanical stress between six- and twelve-weeks post-surgery, as it undergoes necrosis and cellular repopulation, making it mechanically weaker (74-76). Excessive loading during this phase may compromise graft healing, raising concerns regarding the early implementation of HLRT (91). However, in addition to external training load, several other factors influence ACL graft strain, including the type of resistance training (closed vs. open kinetic chain), the degree of knee flexion during exercise, and neuromuscular control (92-96). Although clinical studies have reported no significant differences in ACL graft laxity between strength training with different external training loads, imaging and histological studies assessing the impact

of strength training on ACL graft healing remain lacking (97, 116). Regarding the impact on the knee joint, findings from **Chapter 5** indicate that HLRT is associated with a higher incidence of knee pain, joint effusion, and range of motion deficits compared to LL-BFRT. These findings are clinically relevant, as knee pain management, joint effusion control, and range of motion are essential throughout all phases of rehabilitation. Knee pain and joint effusion can negatively affect proprioception and contribute to arthrogenic muscle inhibition, thereby limiting strength development and delaying functional recovery (117-120). Additionally, deficits in range of motion, particularly in knee extension, are associated with altered gait mechanics, increased joint stress, and a higher risk of long-term functional impairments (121, 122). **Chapter 6** further suggests that LL-BFRT may be a more suitable rehabilitation option, as the increased incidence of knee pain and joint effusion observed in the HLRT group may adversely affect mid- and late-stage rehabilitation milestones, including return to running and on-field sport-specific training. The reduced mechanical stress on the knee joint during LL-BFRT, combined with its potential analgesic effects via exercise-induced hypoalgesia, supports its role as a promising strategy within postoperative rehabilitation (123-125). While LL-BFRT offers promising benefits in muscle strengthening with reduced mechanical load on the knee joint, its safety must be considered carefully. As previously discussed, a key physiological mechanism of LL-BFRT is the occlusion of venous outflow, leading to metabolite accumulation and the recruitment of fast-twitch muscle fibers (108-110). However, this venous occlusion can induce acute cardiovascular changes, including increases in heart rate and blood pressure (126-130). Although these changes are generally lower than those observed in HLRT, they are influenced by factors such as cuff pressure and occlusion duration (129-132). In healthy individuals, these transient cardiovascular responses are typically well tolerated. However, they may pose potential risks for individuals with pre-existing cardiovascular conditions (133). This underscores the importance of pre-intervention screening to identify those at heightened risk of adverse effects (134). Furthermore, to minimize the likelihood of adverse effects, it is crucial to apply LL-BFRT in accordance with established guidelines (100, 135). However, even with proper adherence to guidelines, side effects such as fainting, as described in **Chapter 5**, may still occur. Although these occurrences are rare in healthy individuals, with an incidence of less than 4%, factors such as pain from mechanical stress caused by the cuff, psychological stress or anxiety, and lack of prior exposure to LL-BFRT can contribute to adverse responses (135-138). Monitoring a patient's response to LL-BFRT is essential to detect any signs of adverse effects early and allow for necessary adjustments to ensure safety. Additionally, a structured familiarization phase is recommended before engaging in LL-BFRT, involving initial shorter occlusion durations and lower cuff pressures. By implementing a stepwise introduction to LL-BFRT and closely monitoring patient responses, clinicians can reduce the risk of adverse events and enhance patient comfort. Thus, the implementation of LL-BFRT in rehabilitation aims to safely optimize muscle strength to support a safe return to

sport, enhance patient-reported knee function, and improve overall satisfaction. However, further research is needed to establish its long-term efficacy and safety.

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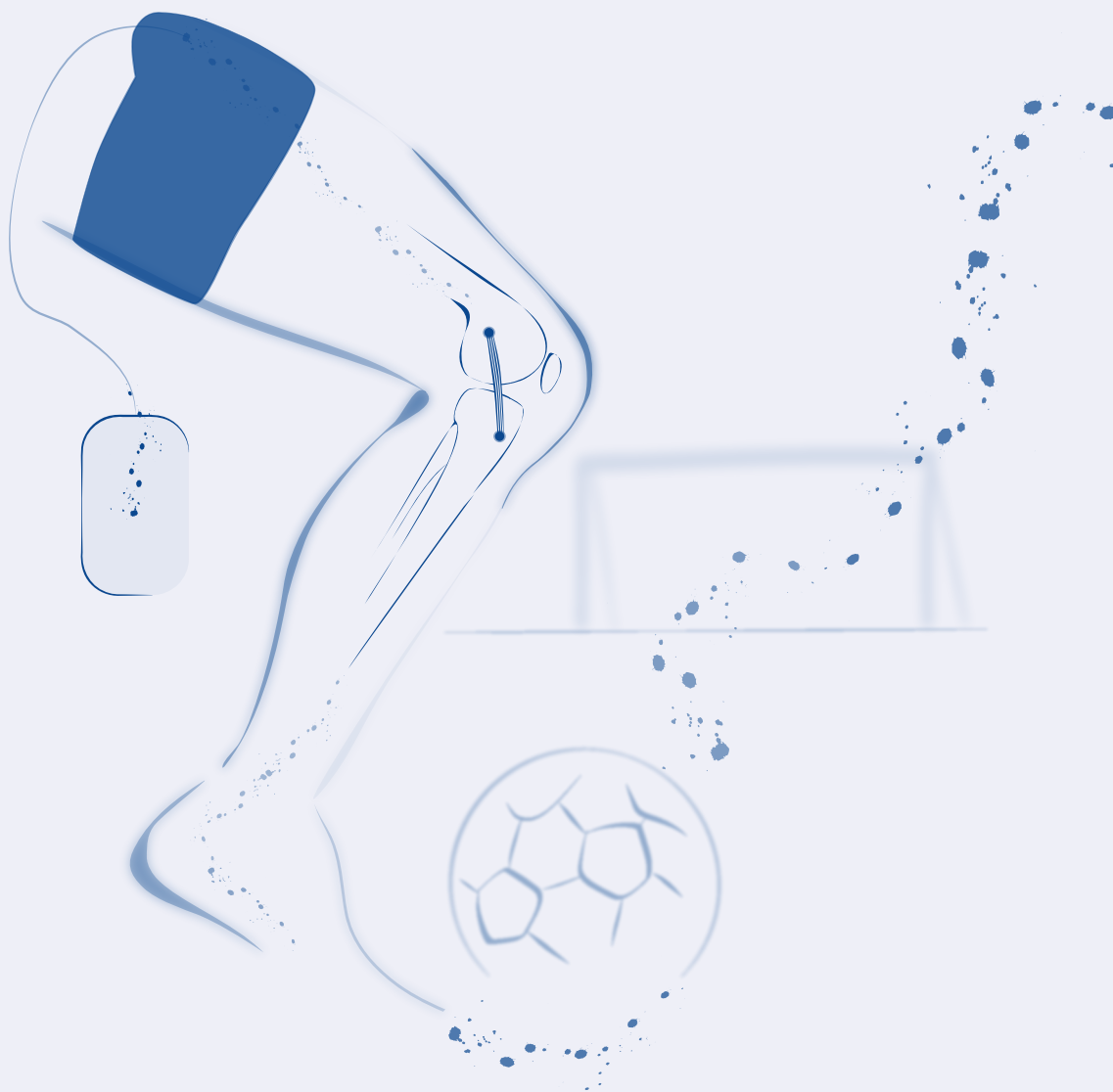
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# Chapter 8



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**Impact paragraph**

## Impact paragraph

The incidence of anterior cruciate ligament (ACL) injuries has increased significantly in recent decades, both in the Netherlands and worldwide (1-3). This increase is particularly evident among adolescents and young adults participating in pivoting sports (1, 2). As a result, ACL reconstruction has become one of the most frequently performed orthopedic procedures. However, although ACL reconstruction aims to facilitate return to pre-injury levels of sport, evidence shows that only 65% of individuals achieve this goal (4, 5). Additionally, ACL graft re-rupture rates of up to 10% have been reported among athletes (3, 6). These findings indicate that current clinical outcomes following ACL reconstruction are suboptimal. Moreover, the increasing incidence of ACL injuries and reconstructions puts growing pressure on healthcare professionals, including physiotherapists and orthopedic surgeons. This highlights the urgent need for improved clinical decision-making, advancements in surgical techniques, and the development of effective rehabilitation strategies to optimize patient outcomes.

To address these challenges, it is essential to develop a comprehensive understanding of current clinical practice and outcomes related to ACL reconstruction. Gaining insight into the present situation is crucial to better prepare for the future. Therefore, this thesis examined trends in ACL reconstruction in the Netherlands, with a focus on graft selection and methods of femoral tunnel placement. Furthermore, it investigated predictors of patient satisfaction following ACL reconstruction and explored the potential benefits of low-load blood flow restriction training (LL-BFRT) in postoperative rehabilitation.

When performing an ACL reconstruction, surgeons must make several important decisions that influence the success of the procedure. Among these are the selection of graft type and the method of femoral tunnel placement. **Chapter 2** showed that most orthopedic surgeons in the Netherlands prefer using hamstring tendon (HT) autografts for primary ACL reconstruction. It also highlighted that the anteromedial and outside-in techniques are favored for femoral tunnel placement, as they allow for more anatomical positioning compared to the traditional transtibial approach.

Currently, graft selection in ACL reconstruction is largely determined by the surgeon's experience and familiarity, rather than by patient-specific factors. While this experience-based approach may offer consistency, it does not adequately reflect the diversity and complexity of today's ACL patients. In my opinion, we can no longer justify such a one-size-fits-all strategy in a field that increasingly prioritizes personalized care. I believe that graft choice should instead be individualized, taking into account patient characteristics such as age, type and level of sports participation, as well as injury-related factors such as concomitant lesions. Therefore, I emphasize the need to move beyond daily routine and to

implement a patient-tailored approach to graft selection in ACL reconstruction to optimize outcomes and ensure high-value, individualized care.

With regard to femoral tunnel placement, **Chapter 2** demonstrated that surgeons favor techniques that allow for more anatomical positioning (7). The preference for these techniques is based on the understanding that anatomical tunnel placement more effectively restores knee biomechanics, enhances joint stability, and reduces the risk of graft failure or the need for revision procedures compared to non-anatomical techniques (8, 9). Such outcomes not only benefit the individual patient by improving recovery and quality of life, but also contribute to a more efficient, sustainable, and cost-effective healthcare system.

Despite clear evidence that anatomical femoral tunnel placement is essential for successful ACL reconstruction, suboptimal positioning still occurs in approximately 20% of cases (10). This inaccuracy in tunnel placement underscores the need for change. I am convinced that we must move beyond the current limitations and make computer-assisted navigation applicable to ACL reconstruction. In knee prosthetic surgery, such technology is already increasingly used and has demonstrated improvements in surgical precision. However, these systems have been developed primarily for arthroplasty, and their application in ACL reconstruction remains limited to pilot studies.

I therefore recommend that more attention and dedicated effort be directed towards optimizing computer-assisted navigation for ACL reconstruction. To achieve this, close collaboration with industry partners will be essential, ensuring that these technologies are refined to meet the specific demands of ligament surgery. Such efforts are crucial to move these technologies from research to routine clinical practice. Ultimately, this will enhance surgical precision and improve patient care. However, surgical technique alone is not enough. As demonstrated in **Chapter 3**, patient satisfaction following ACL reconstruction also depends on effective rehabilitation and return to sport (RTS) without sustaining a second ACL injury. Therefore, it is crucial for surgeons to look beyond the surgical procedure and collaborate with other healthcare professionals to optimize the rehabilitation process and improve patient outcomes.

With growing interest in low-load blood flow restriction training (LL-BFRT), efforts have been made to explore its potential role in enhancing postoperative rehabilitation following ACL reconstruction. **Chapter 4** identified the absence of a standardized LL-BFRT protocol and highlighted the limited evidence. In **Chapter 5**, an evidence-based, criteria-driven LL-BFRT protocol was implemented following ACL reconstruction. This protocol resulted in muscle strength outcomes comparable to those achieved with heavy-load resistance training (HLRT), which is currently considered the gold standard for improving muscle strength. **Chapter 6** further demonstrated that knee pain associated with HLRT may delay

key rehabilitation milestones, including walking without crutches and returning to running, when compared to LL-BFRT.

Based on these findings, I recommend implementing LL-BFRT in the early postoperative phase (the first weeks following ACL surgery) to counteract muscle atrophy and protect the healing knee joint. As rehabilitation progresses and patients can tolerate higher loads, the program should gradually transition to HLRT. LL-BFRT does not replace current rehabilitation protocols. Instead, it is an important addition in the early weeks following ACL reconstruction. It bridges the gap until patients are able to tolerate HLRT safely.

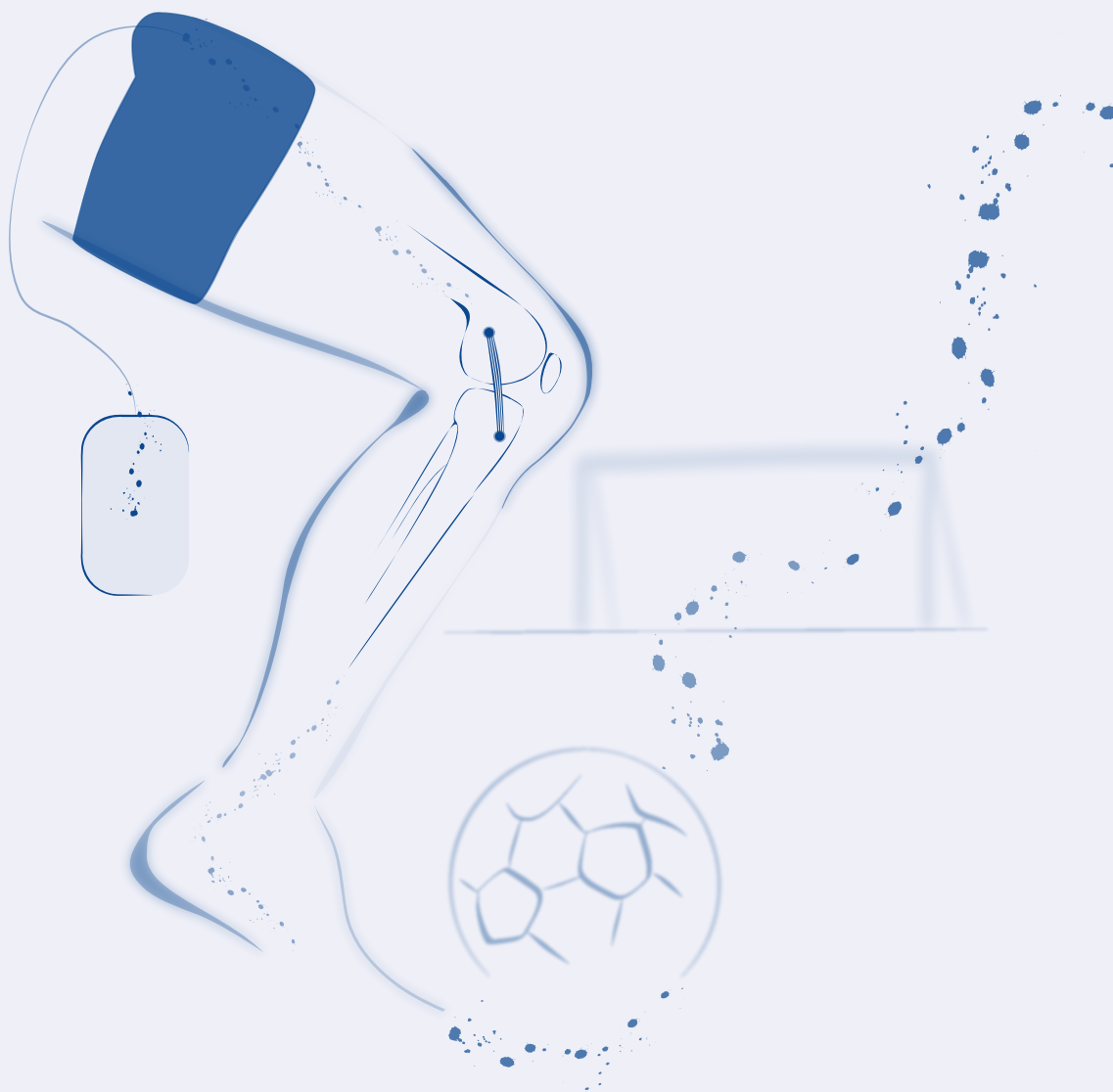
Beyond ACL rehabilitation, I advocate expanding the use of LL-BFRT to broader clinical and performance settings. For patients recovering from knee joint preservation procedures such as cartilage repair and meniscal transplantation, LL-BFRT can restore muscle strength while protecting the knee joint from excessive mechanical stress. In older adults, LL-BFRT is essential for preserving muscle mass and maintaining independence, two key factors in healthy aging and quality of life. In athletes, its integration into training programs can improve performance such as speed, power, and endurance. I am convinced that LL-BFRT should not remain limited to ACL rehabilitation but must be applied widely. A personalized approach will ensure its benefits are optimized across diverse patient populations.

Looking beyond surgery and rehabilitation, the next challenge is predicting outcomes and tailoring management to each individual patient. I am convinced that artificial intelligence (AI) will play a pivotal role in this process. By integrating large-scale data, including patient characteristics, surgical factors, and rehabilitation, AI models can identify patterns and generate individualized predictions about clinical outcomes. These insights can directly support clinical decision-making across the continuum of care, from surgical planning to postoperative rehabilitation and RTS. I argue that AI allows clinicians to move beyond standardized protocols toward personalized medicine. It enables the identification of risk profiles, the optimization of surgical strategies, and individualization of rehabilitation and RTS programs. As AI technology continues to evolve, its role in supporting personalized, efficient, and evidence-based care is expected to grow substantially. I believe that it is necessary to embrace this technology to reduce risks and improve long-term outcomes for patients with ACL injuries.

In conclusion, while the use of computer-assisted navigation and AI in ACL reconstruction remains conceptual at present, their potential to shape a more personalized, patient-centered future in orthopedic care is undeniable. This thesis contributes to that vision by identifying factors that influence surgical outcomes and postoperative recovery. Moving forward, national and international collaboration will be essential to support and accelerate these innovations. Ultimately, integrating human expertise with advanced technologies offers great promise for delivering more effective, patient-centered ACL care.

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# Chapter 10

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**Summary**  
**Samenvatting**

## Summary

Anterior cruciate ligament (ACL) reconstruction is one of the most frequently performed orthopedic procedures worldwide. Despite its widespread use, clinical outcomes remain highly variable and the risk of secondary injury is substantial. These outcomes depend on several factors, including surgical technique, patient characteristics, and postoperative rehabilitation.

To support evidence-based clinical decision-making and improve patient outcomes,, this thesis investigated current ACL reconstruction practices in the Netherlands, identified determinants of postoperative outcomes, and evaluated the potential of low-load blood flow restriction training (LL-BFRT) as a rehabilitation strategy.

### Part I - ACL reconstruction in the Netherlands

**Chapter 2** evaluated current ACL reconstruction practices among members of the Dutch Association of Arthroscopy (NVA). The survey demonstrated a high degree of uniformity in graft selection, with hamstring autografts being used by 87% of surgeons, whereas patellar tendon and quadriceps tendon autografts accounted for only 9% and 4%, respectively. With regard to return to sport (RTS), most surgeons recommended a minimum postoperative period of nine months before clearance. Importantly, this time-based criterion was commonly supplemented by clinical examination, functional performance testing, and patient-reported outcome measures. These findings indicate that graft selection remains largely influenced by surgical training and tradition, whereas RTS decision-making increasingly reflects an individualized and evidence-based approach.

### Part II - Predictors of ACL reconstruction outcome

In **Chapter 3**, predictors of patient satisfaction following ACL reconstruction were investigated in a cohort of 183 patients with a mean follow-up of 3.6 years. Overall, 82% were satisfied with the outcome of surgery. Preoperative and operative factors such as age, body mass index, graft diameter and concomitant meniscal or cartilage interventions did not predict satisfaction. Instead, several postoperative factors were associated with satisfaction. Patients who completed at least nine months of supervised rehabilitation, delayed their return to sport beyond nine months, and did not experience ACL re-injury reported higher satisfaction, as well as better knee function and quality of life. These findings emphasize that postoperative care, particularly supervised rehabilitation and safe return to sport strategies, is crucial for mid-term patient satisfaction following ACL reconstruction.

### Part III - Low-load BFR training post-ACL surgery

Because postoperative rehabilitation emerged a determinant of outcome, the last

part of this thesis focused on LL-BFRT as a strategy to enhance recovery following ACL reconstruction.

**Chapter 4** presented a systematic review investigating the effects of LL-BFRT on quadriceps strength, quadriceps mass, knee joint pain, and ACL graft laxity following ACL reconstruction. A total of six studies involving 152 patients were included. The review compared LL-BFRT with non-BFRT (rehabilitation without blood flow restriction training) and found that LL-BFRT may provide beneficial effects on quadriceps strength and mass. Reduced knee pain was also reported, whereas no differences were observed for ACL graft laxity. However, considerable heterogeneity was present in both LL-BFRT and non-BFRT protocols. The LL-BFRT interventions varied in terms of external training loads (ranging from 0% to 30% of one-repetition maximum (1RM)) and cuff pressure. Similarly, the non-BFRT interventions differed in external training loads, ranging from 0% to 70% 1RM. This variability limits direct comparability between studies.

To address this variability, **Chapter 5** presented a randomized controlled trial comparing LL-BFRT and heavy-load resistance training (HLRT) following ACL reconstruction. All patients followed the same criteria-based postoperative rehabilitation program, with only the strength training component differing between groups. The LL-BFRT group trained at an external load of 30% 1RM combined with individualized cuff pressure set at 80% of limb occlusion pressure, whereas the HLRT group trained at an external load of 70% 1RM. The intervention consisted of 12 weeks biweekly strength training, beginning two weeks after surgery, when patients met the criteria to initiate strength training. Of the 28 patients, 23 completed the intervention. Outcomes were assessed 14 weeks postoperatively, directly after completion of the strength training intervention. Results demonstrated comparable quadriceps and hamstring strength between groups. Secondary outcomes, including knee pain, joint effusion, and range of motion were also similar. Both groups achieved high adherence, with completion rates above 90%. These findings suggest that LL-BFRT is a safe and effective alternative to HLRT in the early rehabilitation following ACL reconstruction. While short-term outcomes were similar, LL-BFRT may offer advantages in terms of reduced mechanical stress on the knee joint.

**Chapter 6** explored patients' experiences with postoperative rehabilitation following ACL reconstruction through a qualitative study. Patients who had undergone rehabilitation with either LL-BFRT or HLRT were interviewed. Participants who completed rehabilitation with LL-BFRT reported experiencing pain during or around strength training less frequently than those who underwent HLRT. Furthermore, they described a favorable rehabilitation trajectory and perceived that they reached rehabilitation milestones earlier. These findings provide valuable insight into patients' experiences and suggest that LL-BFRT may enhance the overall rehabilitation experience following ACL reconstruction.

## Samenvatting

Een voorste kruisband reconstructie behoort wereldwijd tot de meest uitgevoerde orthopedische ingrepen. Ondanks de brede toepassing blijven de klinische uitkomsten variabel en blijft het risico op een recidiefletsel substantieel. Deze uitkomsten worden beïnvloed door meerdere factoren, waaronder operatietechniek, patiëntkarakteristieken en postoperatieve revalidatietraject.

Om evidence-based klinische besluitvorming te ondersteunen en patiëntuitkomsten verder te verbeteren, werden in dit proefschrift de huidige praktijk van voorste kruisband reconstructies in Nederland onderzocht, determinanten van postoperatieve uitkomsten geïdentificeerd en de potentiële meerwaarde van low-load blood flow restriction training (LL-BFRT) als revalidatiestrategie geëvalueerd.

### Deel I - Voorste kruisband reconstructie in Nederland

**Hoofdstuk 2** beschrijft een enquête onder leden van de Nederlandse Vereniging van Arthroscopie (NVA) naar de huidige praktijk rondom primaire voorste kruisband reconstructies. De resultaten lieten een hoge mate van uniformiteit zien in de keuze van graft. Hamstring autografts werden gebruikt door 87% van de chirurgen, terwijl patellapees- en quadricepspees autografts respectievelijk door 9% en 4% van de chirurgen werden toegepast. Ten aanzien van sporthervatting adviseerde de meerderheid van de chirurgen een minimale revalidatieduur van negen maanden alvorens sporthervatting toe te staan. Dit tijds criterium werd doorgaans aangevuld met klinisch onderzoek, functionele testen en patiënt gerapporteerde uitkomstmaten. Deze bevindingen suggereren dat de keuze van de graft wordt beïnvloed door opleiding en traditie, terwijl beslissingen omtrent sporthervatting in toenemende mate een geïndividualiseerde en evidence-based benadering weerspiegelen.

### Deel 2 - Determinanten van uitkomsten na voorste kruisband reconstructie

**Hoofdstuk 3** onderzocht voorspellers van patiënttevredenheid na een voorste kruisband reconstructie in een cohort van 183 patiënten met een gemiddelde follow-upduur van 3,6 jaar. In totaal was 82% van de patiënten tevreden met het resultaat van de ingreep. Preoperatieve en operatieve factoren, waaronder leeftijd, body mass index, graftdiameter en begeleidend meniscus- of kraakbeen interventies, bleken geen voorspellers van patiënttevredenheid. Daarentegen waren verschillende postoperatieve factoren wel geassocieerd met patiënttevredenheid. Patiënten die ten minste negen maanden begeleidde revalidatie hadden gevolgd, hun terugkeer naar sport hadden uitgesteld tot minimaal negen maanden postoperatief en geen recidief voorste kruisbandletsel hadden doorgemaakt, rapporteerden een hogere patiënttevredenheid, een betere kniefunctie en

een hogere kwaliteit van leven. Deze bevindingen onderstrepen het belang van optimale postoperatieve zorg, met name langdurige begeleide revalidatie en een veilige terugkeer naar sport, ter optimalisatie van de uitkomsten na een voorste kruisband reconstructie.

### Deel 3 - Low-load BFR training na voorste kruisband reconstructie

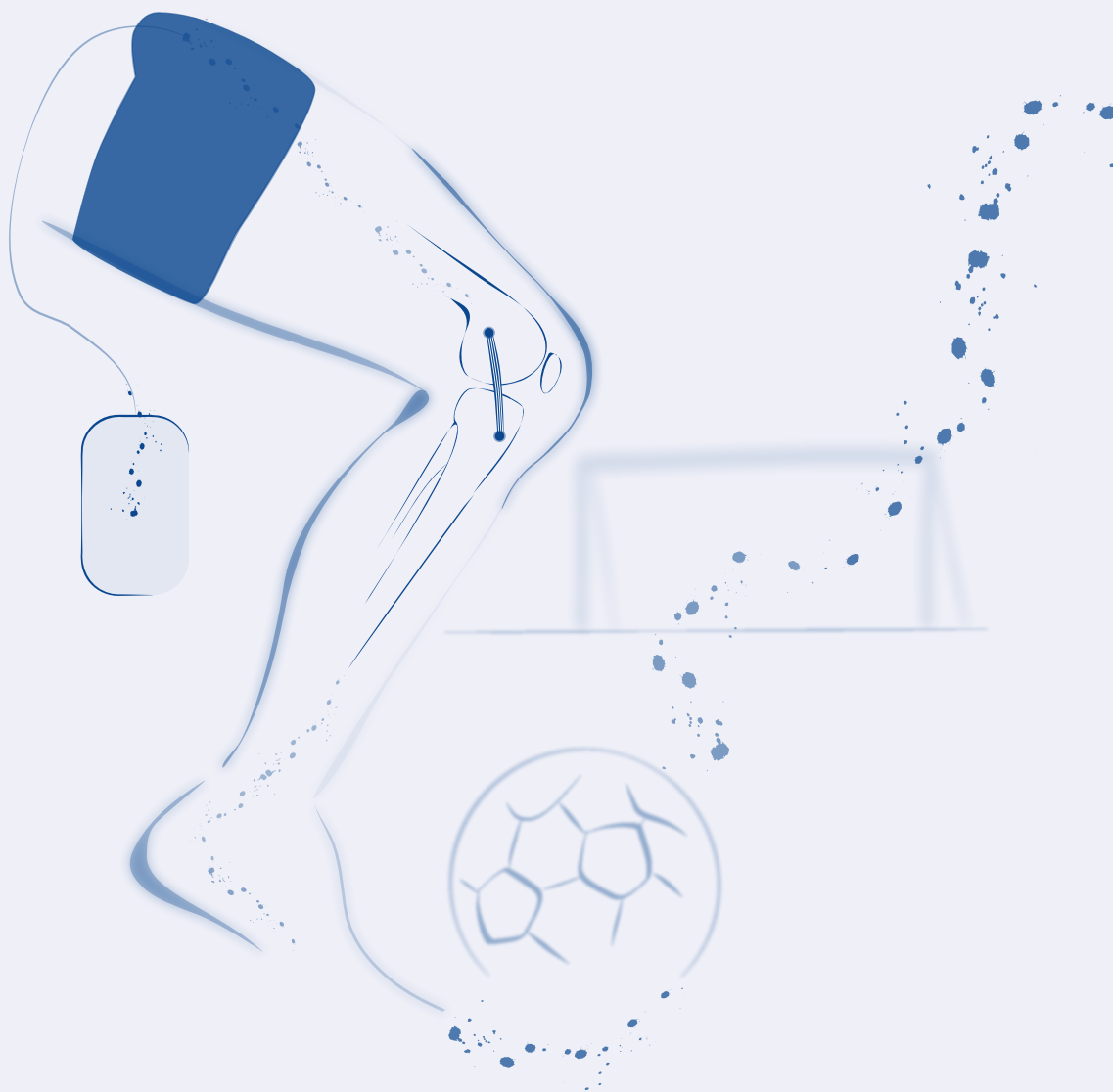
Omdat postoperatieve revalidatie naar voren kwam als een belangrijke determinant van de uitkomsten, richtte het laatste deel van dit proefschrift zich op LL-BFRT als strategie om het herstel na voorste kruisband reconstructie te bevorderen.

**Hoofdstuk 4** presenteerde een systematische review naar de effecten van LL-BFRT op quadricepskracht, quadricepsmassa, kniepijn en voorste kruisband graftlaxiteit. In totaal werden zes studies met 152 patiënten geïncludeerd. De review vergeleek LL-BFRT met conventionele revalidatie zonder blood flow restriction training en liet zien dat LL-BFRT mogelijk gunstige effecten heeft op quadricepskracht en quadricepsmassa. Daarnaast werd minder kniepijn gerapporteerd, terwijl geen verschillen werden gevonden in graftlaxiteit. De geïncludeerde studies vertoonden echter aanzienlijke heterogeniteit. De LL-BFRT protocollen verschilden onder meer in externe trainingsbelasting (variërend van 0% tot 30% van het één-herhalingsmaximum (1RM)) en in toegepaste cuffdruk. Ook de controlegroepen vertoonden grote variatie in trainingsbelasting (variërend van 0% tot 70% van het 1RM). Deze heterogeniteit beperkte de directe vergelijkbaarheid tussen de studies.

Om deze heterogeniteit te ondervangen, presenteerde **Hoofdstuk 5** een gerandomiseerde gecontroleerde studie waarin LL-BFRT werd vergeleken met heavy-load resistance training (HLRT) tijdens de revalidatie na een voorste kruisband reconstructie. Alle patiënten volgden hetzelfde criteria-gebaseerde postoperatieve revalidatieprotocol, waarbij uitsluitend het krachttreiningsonderdeel tussen beide groepen verschild. De LL-BFRT groep trainde met een externe belasting van 30% van het 1RM, gecombineerd met een geïndividualiseerde cuffdruk ingesteld op 80% van de limb occlusion pressure, terwijl de HLRT groep trainde met een trainingsbelasting van 70% van het 1RM. De interventie bestond uit twaalf weken krachttreiningsonderdeel, tweemaal per week, en startte twee weken postoperatief zodra patiënten voldeden aan de criteria om met krachttreiningsonderdeel te beginnen. Van de 28 geïncludeerde patiënten voltooiden 23 de interventie. De uitkomsten werden veertien weken postoperatief geëvalueerd, direct na afronding van het krachttreiningsprogramma. De resultaten toonden vergelijkbare quadriceps- en hamstringkracht in beide groepen. Ook secundaire uitkomsten, waaronder kniepijn, gewrichtseffusie en bewegingsuitslag, verschilden niet tussen de groepen. De therapietrouw was hoog, met een voltooiingspercentage van meer dan 90%. Deze bevindingen suggereren dat LL-BFRT tijdens de vroege revalidatiefase een veilig en effectief alternatief kan zijn voor HLRT na een voorste kruisband reconstructie. Hoewel de korte termijn resultaten vergelijkbaar waren, kan LL-BFRT een aantrekkelijk alternatief vormen voor patiënten die in de vroege postoperatieve fase nog niet in staat zijn met hoge trainingsbelastingen te oefenen.

**Hoofdstuk 6** onderzocht de ervaringen van patiënten met de postoperatieve revalidatie na een voorste kruisband reconstructie aan de hand van een kwalitatieve studie. Patiënten die een postoperatief revalidatietraject hadden gevolgd met LL-BFRT of HLRT werden geïnterviewd. Patiënten die met LL-BFRT hadden gerevalideerd, rapporteerden minder frequent pijn tijdens of rondom krachttraining dan deelnemers die met HLRT hadden gerevalideerd. Daarnaast beschreven zij een gunstiger revalidatieverloop en hadden zij de perceptie dat zij revalidatiemijlpalen eerder bereikten. Deze bevindingen bieden waardevol inzicht in de ervaringen van patiënten tijdens het revalidatieproces en suggereren dat LL-BFRT de revalidatie ervaring na een voorste kruisband reconstructie positief kan beïnvloeden.





# Addendum

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**Dankwoord**  
**Curriculum Vitae**  
**List of publications**

## Dankwoord

Een promotietraject wordt vaak omschreven als een wetenschappelijke reis. Voor mij was het vooral een bijzondere periode, gevuld met inspirerende ontmoetingen, mooie samenwerkingen en onvergetelijke momenten. Van de polikliniek en de operatiekamer tot de vergaderingen, congreszalen en de gezelligheid daarbuiten. Het zijn vooral de mensen die deze jaren zo waardevol hebben gemaakt.

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Mijn eerste woorden van dank gaan uit naar mijn promotor, **prof. dr. R.A. de Bie**, en mijn copromotoren, **dr. E.J.P. Jansen** en **dr. M.G.M. Schotanus**. Jullie hebben mij de afgelopen jaren met veel vertrouwen, enthousiasme en betrokkenheid begeleid. Dankzij jullie heb ik niet alleen dit proefschrift kunnen realiseren, maar heb ik mij ook kunnen ontwikkelen tot de arts en onderzoeker die ik vandaag ben. Daar ben ik jullie ontzettend dankbaar voor.

Beste **Rob**, dank voor de kansen die je mij de afgelopen jaren hebt gegeven en voor de prettige manier waarop je mij hebt begeleid. Je gaf mij het vertrouwen en de ruimte om mijn eigen ideeën te ontwikkelen, maar stond altijd klaar om mee te denken en de juiste vragen te stellen. Met jouw toegankelijkheid, oprechte interesse en kritische blik wist je mij steeds opnieuw uit te dagen. Daarbij maakten jouw humor en relativiseringsvermogen iedere bespreking niet alleen leerzaam, maar ook bijzonder aangenaam.

Beste **Edwin en Martijn**, als ik terugkijk op de afgelopen jaren, kan ik me mijn opleiding en dit promotietraject eigenlijk niet voorstellen zonder jullie. Jullie hebben mij niet alleen enthousiast gemaakt voor de orthopedie en de wetenschap, maar zijn door de jaren heen ook veel meer geworden dan alleen collega's en begeleiders. Met jullie betrokkenheid, steun en de vele gesprekken hebben jullie een belangrijke plaats ingenomen in mijn opleiding en loopbaan. Ik besef me dat ik veel aan jullie te danken heb.

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**Marion**, bedankt voor de nauwgezette en gedetailleerde literatuursearch voor de review studie. Met jouw gestructureerde aanpak, oog voor detail en bijna magische vingers op het toetsenbord liet je de literatuursearch vaak eenvoudiger lijken dan ze daadwerkelijk is. Achter die ogenschijnlijke vanzelfsprekendheid gingen echter talloze uren van nauwgezet werk en toewijding schuil. Jouw bijdrage vormde een onmisbare basis voor het verdere verloop van het project. **Alexander**, bedankt voor de fijne samenwerking tijdens het screenen en includeren van de artikelen. Het was geruststellend om vast te stellen dat we onafhankelijk van elkaar exact dezelfde keuzes maakten. Onze consensusgesprekken waren daardoor vaak sneller afgerond dan de tijd die nodig was om ze in te plannen. Ik kijk met veel plezier terug op de samenwerking en de vele leuke momenten onderweg.

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## Curriculum Vitae

Bariş Beytullah Koç was born in Genk, Belgium. He studied Medicine at Maastricht University. From 2017 to 2023, he completed his residency in Orthopedic Surgery within ROGO Zuid-Limburg at Maastricht University Medical Center (MUMC+), VieCuri Medical Center, and Zuyderland Medical Center. During his residency, he developed a particular interest in knee surgery, combining clinical practice with scientific research focused on anterior cruciate ligament reconstruction and rehabilitation.

Following his orthopedic residency, he completed fellowship training in knee arthroplasty and joint preservation surgery at Ziekenhuis Oost-Limburg (Belgium) and University Medical Center Utrecht (the Netherlands). He subsequently broadened his expertise through international fellowships at Acibadem (Turkey), University of Pittsburgh Medical Center (United States), Ospedale Sacro Cuore Don Calabria (Italy), and Aspetar (Qatar).

Alongside his clinical career, he has remained actively involved in research and medical education. His work has been recognised through several grants, including the Dr. C.J. Vaillant Research Grant and the Pennsylvania Orthopedic Society Foundation Grant.

He currently works as an orthopedic surgeon at Ziekenhuis Oost-Limburg, Belgium, specialised in knee arthroplasty and joint preservation surgery.

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