

## · 国外专家笔谈 ·

## Knee Ligament Surgery : The Pittsburgh Opinion

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Freddie H. Fu M.D. (傅浩坚)教授,医学博士,男,51岁,美籍华人。现任美国匹兹堡大学医学院骨科主任,美国骨科医师学会及运动医学学会会员,《中国微创外科杂志》编辑委员会国际顾问委员。专长于骨创伤及运动损伤的治疗研究工作,尤其在膝关节运动创伤的基础研究及治疗方面有突出成果。在国际知名刊物上发表《前交叉韧带重建术趋势》等论文 110 余篇,主编及撰写《膝关节外科学》等专著 20 余部,参加了《肌肉骨骼系统手术学》等 60 余册骨科专著的编写,担任《骨与关节疾患》、《美国运动医学杂志》等数十家知名骨科和运动医学刊物的编委,是世界著名的骨科和运动医学专家。

## 膝关节韧带外科——匹兹堡观点

北京大学第三医院运动医学研究所 印钰 摘译

膝关节前交叉韧带重建手术已广泛在全球开展。现在其有 20 种以上的手术方法和至少 5 种移植物被经常应用。最常用的髌腱(B-P-B)和腓绳肌腱均不能达到重建止点结构、恢复生物力学特性以及神经反射功能的目的。尤其是腓绳肌腱由于固定点和内固定物的影响更难达到上述完美要求。

以下是匹兹堡大学医学院骨科对前交叉韧带重建的几点认识及展望:

1. 通过体外移植物生物力学研究,我们发现常用移植物在解剖重建前交叉韧带(分前内束、后外束)后的抗旋转负荷能力明显增强。在 Lachman 试验和轴移试验中的自身张力接近正常韧带。同时胫骨处移植物的固定位置离关节面越近,膝关节的稳定性越好。目前还不能明确是哪种康复程序能最有效地使移植物承担负荷而又不超过自身内固定的力量。希望通过移植物和正常交叉韧带负荷情况下的受力参数对比来检查移植物的功能,并指导手术后的康复,这是我们所认为的前交叉韧带重建的真正金标准。

2. 生物学方面韧带移植物在形成强有力的纤维组织以前需要经过炎症、部分坏死、再血管化、成纤维细胞重新植入以及逐渐塑型和胶原结构的不断改变来完成重建过程。韧带移植物在这个过程中仅起模板作用。而传统的移植物在手术后 6 个月内都不可能恢复正常的韧带止点 4 层结构。我们考虑用基因治疗、细胞治疗或组织工程学方法,通过导入治疗基因或编码的生长因子,如 BMP-2, TGF- $\beta$  等进入细胞和组织,来促进移植物的生物学愈合、塑型重建、恢复神经血管功能。

3. 另外借助影像学技术的进步和计算机辅助骨科手术系统的应用,医生的手术技巧将会进一步提高,使上下止点的定位更准确,减少手术中错误操作的发生率。根据患者的不同情况采用不同的手术方法和康复程序仍然是目前手术医生的工作重点,而生物力学和生物学新技术的开发应用在以后的十年内将变得更为重要。

## Introduction

In spite of the large number of anterior cruciate ligament (ACL) reconstructions that are being performed each year around the world (estimated between 75,000 to 100,000 cases in the United States alone), the question remains: "how perfect are current operative techniques?" The fact that many new techniques have been

reported in the literature, success rates for long-term clinical outcome can still not exceed 85% - 90%<sup>[1-3]</sup>. The global perspective on ACL reconstruction shows that more than 20 different surgical techniques are available today, that more than five different grafts are currently being used with different rehabilitation protocols and different outcome assessments. At the recently held Panther Sports Medicine Symposium (Pittsburgh, PA, USA, May 4-6, 2000), 14 specialists in knee ligament reconstruction presented their graft

choice and preferred technique for ACL reconstruction on a global panel consisting of experts from five continents. Interestingly, about 50% of the experts were in favor of the hamstring tendons, 50% preferred the B – PT – B graft, and two – thirds of the surgeons use multiple grafts. There was a discussion about several possibilities for fixation of grafts that have undergone an evolutionary process in the past two decades. Especially for hamstring tendons we still have not found the perfect solution yet. However, talking about different grafts keeps us from addressing the real dilemma: “the perfect graft does not yet exist!” This perfect graft would reproduce insertion sites and biomechanics, provide biological incorporation, and resume neuromuscular control.

Looking into the ideology of possible failures, three major points have to be discussed. The surgical techniques are obviously one reason for so – called misplacement of tunnels, inferior ultimate load and stiffness of graft constructs combine for biomechanical considerations and finally biological reasons like tendon – bone healing, graft remodeling and graft incorporation have to be taken into account.

### Biomechanics :

During the last decade, significant efforts have been made to quantify the forces and strains in the ACL in vitro as well as in vivo settings. As result, various devices and methods have been developed to measure the force and strain in ligamentous tissue. In our laboratory, we have successfully used a 6 – degree of freedom (DOF) universal force moment sensor (UFS) in combination with a 6 – DOF robotic manipulator to measure the in situ force of the ligament<sup>[4-7]</sup>. This method is based on the robot reproducing positions such that the principle of superposition can be employed to calculate changes in forces and moments of a ligament before and after it is transected. Advantages of this robotic/UFS testing system are that it does not depend on the specimen geometry or the location of the ligament to make the necessary measurements, and that the in situ forces in the ACL are determined without having a device physically contact the ligament. Forces and distributions in both the AM and the PL bundle of the ACL have been quantified during the anterior drawer test, Lachman test and simulated pivot shift test using human cadaveric knee specimens<sup>[8,9]</sup>. We learned that a tibial graft fixation nearest the articular surface resulted in a more stable knee and closer in situ forces to the intact ACL<sup>[10]</sup>. We also found that the position of the tibia during graft fixation had a significant effect on the biomechanical outcome<sup>[11]</sup>. Two popular grafts for ACL reconstruction, quadruple semitendinosus/ gracilis (hamstrings) and bone – patellar tendonbone were studied<sup>[12]</sup>. Both were found to have little improvement over the ACL deficient knee when rotational loads were applied. Whereas, an anatomical reconstruction replacing the AM and PL bundles resulted in knee kinematics significantly closer to those in the intact ACL as compared to conventional reconstruc-

tion procedures<sup>[13]</sup>. Additionally, the in situ forces in the anatomical reconstruction were substantially closer to those of the intact ACL compared when the knee was subjected to both the Lachman and simulated pivot shift tests. However, what we still need are in – vivo forces in ligaments to reveal which postoperative rehabilitation protocol is the most effective in loading the ACL graft but not exceeding the fixation strength. Furthermore, knowledge of in – vivo forces of the ACL will enable us to examine the function of the ACL grafts by comparing the force data with those for the intact ACL – which we consider as the “true gold standard” to achieve for ACL reconstruction.

### Biological Aspects :

After ACL – reconstruction, tendon grafts undergo biologic modifications before they form strong fibrous tissue. In the beginning, the graft undergoes inflammation and (partial) necrosis. The graft then undergoes revascularisation and repopulation with fibroblasts. The last stage is marked by a gradual remodeling of the graft and continuous modification of its collagenous structure<sup>[14,15]</sup>. There is evidence that autograft as well as allograft transplants are repopulated with extrinsic fibroblast within four weeks<sup>[16]</sup>. After four to six weeks, the graft is completely repopulated. Donor fibroblasts undergo cell death and are not detectable thereafter. The tendon structure, however, serves as a template for soft tissue remodeling<sup>[17,18]</sup>. While the biology of healing of the ACL replacement graft is grossly the same for all biologic graft materials, graft fixation is unlike for different graft tissues. Grafts with bone plugs on either side (bone – patella tendon – bone (BPTB), quadriceps tendon) allow for bone – to – bone healing within the bone tunnels. Soft tissue grafts, however, such as the quadruple semitendinosus/ gracilis tendon graft, have a different healing process, with tendon – to – bone healing within the bone tunnels<sup>[19,20]</sup>.

With the advent of accelerated rehabilitation after ACL reconstruction, the demand for higher fixation strength to withstand early mobilization has also increased<sup>[21]</sup>. The initial strength of a replacement graft is provided by the fixation device, such as the interference screw, which is the fixation device of choice for B – PT – B graft fixation. For hamstring tendons on the other hand, there are numerous fixation devices available, endobutton, cross pin, staple, suture post are some of them. bioabsorbable screws have been introduced in recent years and the material properties are comparable with metal interference screws<sup>[22,23]</sup>. Bioabsorbable screws can lead to an accelerated tendon – bone healing with a press – fit fixation of hamstring tendons in the bone tunnels<sup>[24]</sup>, however, the fixation of the tendon is at risk by time of bioabsorption of the screw and can be a potential cause of failure<sup>[25]</sup>. The solution for the clinical practice is a tailor made rehabilitation protocol, whereby the individual reconstruction technique as well as the patients ability to follow the rehabilitation proto-

col are respected. Graft tunnel motion and bone tunnel enlargement are phenomena that have both biomechanical and biological backgrounds. The longitudinal, or bungee cord like graft tunnel motion is seen in hamstring graft fixation with polyester tape – titanium button – technique. In a cadaveric study, graft tunnel motion of 1 to 3 mm occurred under physiologic loading of 100 to 300 N, with the majority of motion contributed from the polyester tape loop<sup>[26]</sup>. The distance of the point of graft fixation from the joint is an important factor for sagittal graft tunnel motion of the windshield wiper effect. In a porcine study, the greater the distance of the point of graft fixation from the joint was, the greater the resultant anterior laxity of the graft construct was<sup>[10]</sup>.

Normal insertion site anatomy of the ACL has a specific arrangement of collagen fibers, fibroblasts, fibrochondroblasts and osteoblasts forming a direct ligament insertion, which consists of four layers. The first layer comprises the ligament, the second layer is characterized as a nonmineralized cartilage zone containing fibrocartilaginous cells, the third layer is the mineralized cartilage zone, where the mineralized cartilage inserts into the subchondral bone plate, the fourth layer, to which the ligament is attached (Figure 1). The design of this complex insertion site allows for distribution of longitudinal and shear forces from the ligament into the subchondral bone plate, thus minimizing stress on single collagen bundles<sup>[27]</sup>. This complex anatomy, however, is not restored by conventional ACL – transplantations within the first six month after graft implantation.

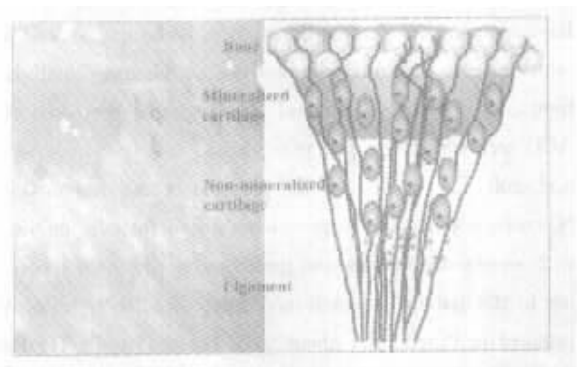


Figure 1 ACL – insertion, four zones  
(left: histology, right: schematic)

## Biological Solutions:

Presently, no graft can reproduce the normal insertion sites and grafts undergo a certain remodeling process, the question remains how to improve healing and remodeling. The biological approaches might apply tissue engineering, gene therapy and cell therapy. Various growth factors have been identified to affect the healing process in tissue of the musculoskeletal system like the ACL<sup>[28]</sup>. Growth factors are small peptides that can be synthesized both by

the resident cells at the injury site (e.g. fibroblasts, endothelial cells, mesenchymal stem cells) and by the infiltrating reparatory or inflammatory cells (e.g. platelets, macrophages, monocytes). They are capable of stimulating cell proliferation, migration and differentiation as well as the matrix synthesis<sup>[29-30]</sup>. Meanwhile, the stimulating effect of various growth factors in different tissues has been demonstrated<sup>[31-33]</sup>. The gene encoding for most of the known growth factors have been determined and using the recombinant DNA technology, we are now able to produce large quantities of these recombinant proteins for the purpose of treatment.

Although the direct application of human recombinant proteins has some beneficial effect on the healing process, very high dosages and repeated injections of these proteins are often required due to their relatively short biological half-life. Another major limitation of using growth factor proteins to promote healing is their delivery to the injured site. In fact, various strategies, including polymers, pumps and heparin have been investigated to achieve constant levels of growth factors at the injured site<sup>[34-35]</sup>. Despite the fact that these approaches have been capable of improving the local persistence of the growth factor proteins, the results of these delivery techniques remain limited. Among the different methods developed for local administration of growth factors, gene transfer techniques have been proven to be the most promising<sup>[36]</sup>.

Gene therapy is a technique that relies on the delivery of therapeutic genes into cells and tissues. Originally, gene therapy was conceived for the manipulation of germ-line cells for the treatment of inheritable genetic disorders, however this method is limited to not yet efficient technology and considerable ethical concerns. Gene therapy can be applied to the field of orthopaedic Surgery by transferring of defined genes encoding for growth factors or antibiotics into a target tissue (e.g. ligament, cartilage or bone), Thus, local cells at the injury site can highly and persistently produce therapeutic substances.

For gene expression, the transferred DNA material has to enter the nucleus, where it either integrates into the chromosomes of the host cells or remains episomal. After transcription, the generated mRNA is then transported outside the nucleus, serving as a matrix for the production of proteins (e.g. growth factors) in the ribosomes (Figure 3).

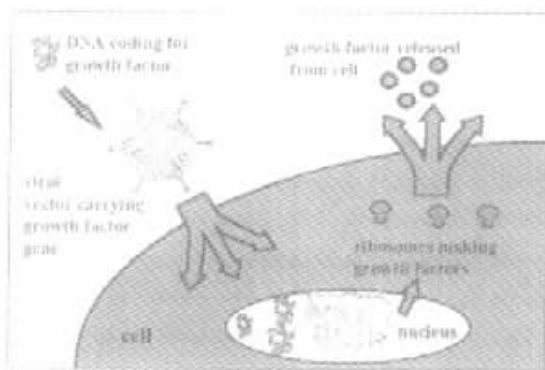


Figure 3 schematic of gene transfer using a viral vector

Consequently, the transduced cells become a reservoir of secreting growth factors and cytokines capable of improving the healing process. Viral (e.g. adenovirus, retrovirus) and non-viral (e.g. liposomes, gene gun) vectors can be used for delivery of genetic material into cells.

Tissue engineering based approaches that aim at using cells from different origin tissues (e.g. mesenchymal stem cells, muscle derived stem cells or dermal fibroblasts) to deliver genes might offer additional opportunities to improve the healing process<sup>[37]</sup>. Selecting the appropriate gene delivery procedure depends upon various factors such as the division rate of the target cells, pathophysiology of the disorder and the accessibility of the target tissues.

### Perspectives :

In the future, improvement of biological incorporation of replacement grafts will lead to better insertion site healing as well as faster ingrowth of the graft. Gene therapy, cell therapy, and tissue engineering are the possible biological tools. It will be possible to deliver therapeutic genes, encoding growth factors, such as BMP-2, TGF- $\beta$ , etc. into cells and tissues. Furthermore, the application of certain growth factors can create any graft type that does enhance biological healing, insertion site incorporation, and restores nerve and vascular function. One focus can be the gene-based cell therapy approach that is based on the ability of mesenchymal stem cells (from blood, bone marrow or muscle) to divide into a variety of cell types. In the future, a simple muscle biopsy may then be enough to provide the cell that can restore any kind of defect in the knee (cartilage) by growing the local cell line (chondrocytes). However, we have to take safety issues into consideration. A new therapeutic approach that might

be extremely promising needs to undergo extensive animal study prior to application on humans.

Additionally, surgical techniques need to be perfected. Improved imaging techniques and computer-assisted orthopedic surgery (CAOS) will enhance both surgical precision and preoperative evaluation. Advantage can thereby be taken of passive navigation systems (Knee Nav<sup>®</sup>, Pittsburgh, USA) as well as active robot system (CASPAR<sup>®</sup>, Rastatt, Germany). Using these newly developed tools we expect to gain more precision in tunnel placement of ACL reconstructions. However, both systems, active and passive, rely heavily on preoperative planning and accurate imaging. But we have to understand that the computer-assisted surgery will only be as precise as the surgeon who plans it. Computer-assisted orthopedic surgery, improved precision, and technical enhancement will again reduce the risk of error in surgery. In the year 2020 we will have improved biomechanical knowledge, sophisticated biological tools, and user-friendly computer-assisted surgery. There is a good chance that a biological/tissue engineered graft will be available. However, in the year 2001, the surgeon still has to focus on perfecting the surgical technique as well as adjusting the rehabilitation protocol to the individual patient. Essentially, a surgeon who performs less than 30 ACL reconstructions per year should use one technique and graft. In contrast, if the practice is more than 50-60 cases a year, the surgeon should hopefully be familiar with several techniques and grafts and apply them according to the patient's needs and interests. In the clinical protocol in Pittsburgh, about 50% Bone-Patella Tendon-Bone, 45% hamstring tendon autografts, and 5% allografts are being used in the year 2001. This varies according to patient requirement. However, in the next decade, the difference in grafts will be less pivotal as biological and biomechanical advancements continue to evolve.

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