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DOI
10.1016/j.bjps.2022.10.036

Publication date
2023

Document Version
Final published version

Published in
Journal of Plastic, Reconstructive and Aesthetic Surgery

Citation (APA)
Puladi, B., Ooms, M., Geijtenbeek, T., Trinler, U., Houschyar, K. S., Gruber, L. J., Motmaen, I., Rashad, A., Hölzle, F., & Modabber, A. (2023). Tolerable degree of muscle sacrifice when harvesting a vastus lateralis or myocutaneous anterolateral thigh flap. *Journal of Plastic, Reconstructive and Aesthetic Surgery*, *77*, 94-103. https://doi.org/10.1016/j.bjps.2022.10.036

Journal of Plastic, Reconstructive & Aesthetic Surgery 77 (2023) 94–103

JPRAS
An International Journal of
Surgical Reconstruction
www.JPRASurg.com

Original Article

Tolerable degree of muscle sacrifice when harvesting a vastus lateralis or myocutaneous anterolateral thigh flap

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Received 22 March 2022; accepted 11 October 2022

KEYWORDS
Flap-raising;
Vastus lateralis muscle flap;
Myocutaneous anterolateral thigh flap;
Predictive forward dynamic simulation;
SCONE

Summary The myocutaneous anterolateral thigh (ALT) and vastus lateralis (VL) flaps include a large muscle mass and a sufficient vascular pedicle, and they have been used for decades to reconstruct traumatic and acquired defects of the head and neck and extremities. In spite of these benefits, musculoskeletal dysfunction was reported in nearly 1 out of 20 patients at follow-up. It is unclear whether the recently proposed muscle-sparing flap-raising approach could preserve VL muscle function and whether patients at increased risk could benefit from such an approach. Therefore, we performed a predictive dynamic gait simulation based on a biological motion model with gradual weakening of the VL during a self-selected and fast walking speed to determine the compensable degree of VL muscle reduction. Muscle force, joint angle, and joint moment were measured. Our study showed that VL muscle reduction could be

Abbreviations: ALT, anterolateral thigh; DS, donor site; BIFEMSH, biceps femoris short head; GAS, gastrocnemius muscle; GLUT, gluteus maximus; HAM, hamstring muscles; HS, healthy side; ILPSO, iliopsoas muscle; QUAD, quadriceps femoris muscle; RF, rectus femoris muscle; SOL, soleus muscle; TA, tibialis anterior muscle; VI, vastus intermedius muscle; VL, vastus lateralis muscle; VM, vastus medialis muscle.

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https://doi.org/10.1016/j.bjps.2022.10.036
1748-6815/

compensated up to a certain degree, which could explain the observed incidence of musculoskeletal dysfunction. In elderly or fragile patients, the VL muscle should not be reduced by 50% or more, which could be achieved by muscle-sparing flap-raising of the superficial partition only. In young or athletic patients, a VL muscle reduction of 10%, which corresponds to a muscle cuff, has no relevant effect. Yet, a reduction of more than 30% leads to relevant weakening of the quadriceps. Therefore, in this patient population with the need for a large portion of muscle, alternative flaps should be considered. This study can serve as the first basis for further investigations of human locomotion after flap-raising.

Introduction

Pedicled or microvascular free flaps are essential for covering traumatic or acquired defects, particularly in the head and neck region and extremities. As a workhorse, the anterolateral thigh (ALT) flap is one of the most raised flaps since its initial description in 1984.[1-3] The perforators of the ALT flap pass through the vastus lateralis (VL) muscle in most cases, which results in a variable involvement of portions of the VL, leading to a myocutaneous ALT flap.[3] The VL itself can also be raised as a pure muscle flap, which, in 1980, was described as a pedicled flap to cover the defects in the lower abdomen and proximal part of the lower extremity[4] and, in 1992, as a microvascular free flap.[5] The VL is one of the four heads of the quadriceps femoris muscle (QUAD), along with the vastus intermedius (VI), vastus medialis (VM), and rectus femoris (RF), and arises largely from the anterior area of the femur and inserts into the patella tendon. It is a knee extensor[6] and is about as strong as the VI and VM combined, contributing to most of the muscle force of the QUAD.[7] It plays a crucial role both in standing and in the normal walking stride.[8]

The advantages of the myocutaneous ALT/VL flap include a large muscle mass and a long vascular pedicle, allowing it to be used both as a pedicled flap and as a microvascular free flap for a variety of reconstructions.[9] Furthermore, muscle or muscle-containing flaps reduce dead space, increase blood flow and resistance to infection, provide functional innervated coverage, and cover exposed vital structures.[10] With the improvement in reconstruction outcomes at the recipient site, the reduction of donor-site morbidity has become an important goal for surgeons.[11] However, the use of the myocutaneous ALT/VL flap has its drawbacks as musculoskeletal dysfunction was found at follow-up in 4.8% of cases.[12,13]

The reason for musculoskeletal dysfunction could be that the VL is thought of as a single muscle, although since the 19th century, there has been evidence that it consists of three distinct partitions, namely, the superficial, intermediate, and deep partition.[11] Each of these partitions represents an average of 42.6% (superficial), 33.9% (intermediate), and 23.5% (deep) of the muscle volume and has its own neural and vascular supply, allowing it to be raised separately as a flap. In this regard, muscle-sparing flap-raising would preserve muscle function of the VL.[11] Therefore, it could be presumed that a patient group at risk of postoperative musculoskeletal dysfunction would benefit from such an approach. However, Toia et al. only described the technique of muscle-sparing flap-raising but did not investigate its likely impact on musculoskeletal function.[11]

Therefore, one could ask whether a tolerable degree of muscle reduction could be determined with respect to a recommended surgical approach. This could help in deciding how many and which partitions can be raised without having a negative impact on the human locomotion.

Yet, experimental surgery with a predefined and gradual muscle reduction would be very difficult and unacceptable from an ethical point of view. However, modeling and simulation of the human neuromusculoskeletal system could help provide insights into the impact of VL muscle reduction on the human locomotion with focus on determining tolerable degrees for muscle reduction.[14,15] In 2010, one mathematical model was developed to produce realistic simulations of human locomotion.[16] The use of this type of simulation enable to work on hypotheses that are otherwise difficult to answer on the basis of clinical data.[14] Therefore, the analysis of what-if-questions about human locomotion is possible.[15]

In this study, the effects of different degrees of VL muscle reduction on human locomotion following VL or myocutaneous ALT flap-raising were examined using predictive dynamic forward simulation to evaluate the presence of a threshold that could prevent musculoskeletal dysfunction and thus help in the clinical decision of muscle-sparing flap-raising (Figure 1).

Methods

Model

We chose a planar-reduced musculoskeletal gait model with 22 muscles and 9 degrees of freedom (Figure 2A). It was based on the standard model with 18 muscles and 9 degrees of freedom from the open-source software SCONE version 2.0.[15] Because the original model did not describe the vasti muscles as three separate muscles, we added the VL, VI, and VM from the gait2392 model.[17] The kinematic and dynamic properties of the model[17-20] and the anatomical data of the model were originally specified in the literature[7,21-25] and were already implemented in the standard SCONE model.

The simulated model was 180 cm tall, weighed 75.16 kg, and contained the following muscles: for the iliac region, the iliopsoas (ILPSO); for the buttocks, the gluteus maximus (GLUT); for the thigh, the hamstrings (HAM); for the biceps, femoris short head (BIFEMSH) and the QUAD represented by

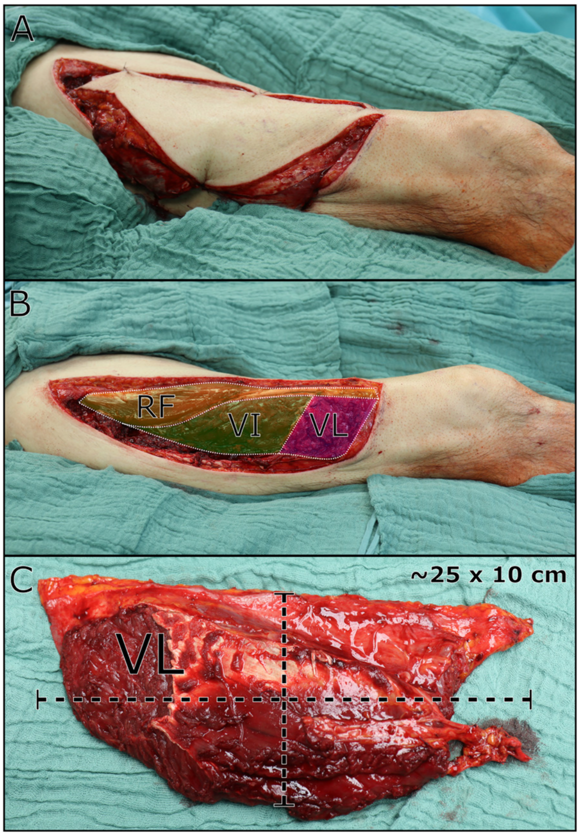

Figure 1 **(A)** A myocutaneous ALT flap raised with a circumscribed skin island on the right anterior thigh before deposition of the supplying vascular pedicle. **(B)** The thigh after raising the myocutaneous ALT flap. Almost the entire vastus lateralis muscle (VL) was raised during this procedure. Rectus femoris muscle (RF) and vastus intermedius muscle (VI) are remaining. **(C)** The raised ALT flap with a large portion of the VL of about 25 $\times$ 10 cm in size.

the VL, VI, VM, and RF; and for the lower leg, the gastrocnemius (GAS), soleus (SOL), and tibialis anterior (TA).

Simulation

We used a muscle reflex model by Greyer and Herr as a controller, which generated the muscle excitation patterns required for locomotion of our musculoskeletal model within the predictive forward dynamic simulation.[16] The initial gait controller for the healthy gait was symmetric (Supplementary Table 1). The optimization was driven by the minimization of metabolic energy expenditure according to Wang et al..[26]

We performed the simulation with a self-selected (i.e., preferred or comfortable walking speed) and a fast gait speed. Beforehand, a common seed with a target speed of 1.5 m/s was used for both walking speeds. Afterward, healthy gait control parameters were optimized for self-selected and fast walking speed. The self-selected walking speed was achieved by adding an objective term that penalizes walking speeds below 0.5 m/s in the gait controller.[27] The fast walking speed was achieved by penalizing walking speeds below 1.7 m/s during the optimization of the gait control parameters. The gait controller was symmetrical to ensure the same motion sequence between the impaired and unimpaired limbs (Figure 2B).

For further simulations, the parameters of the healthy gaits were used after optimization as a seed, but on the basis of an asymmetric gait controller to investigate the influence of a weakened VL muscle on the impaired (right) limb on human locomotion. For this purpose, we reduced the maximum isometric force of the VL muscle at the donor site from 100% to 0% in 10% steps and performed the optimization for both walking speeds. After each simulation, the previous parameters were used as the seed for the next weakening stage. A standard deviation factor of 0.5 was chosen in SCONE to speed up the optimization when a seed was specified. Because a setting of 0% VL muscle force was not possible in SCONE, we chose to set the maximum VL isometric force to 0.01% in this case (Figure 2B).

We measured the effects of the change in maximum isometric muscle force of the VL on the musculoskeletal system of the lower limbs using muscle forces, joint degrees and moments, and gait velocity. These different percentages of maximal isometric force corresponded to partial or complete loss of function of the VL muscle on the impaired limb (Figure 2C). All predictive simulations were performed using the open-source software SCONE version 2.0[15] and accelerated using the proprietary Hyfydy simulation software on the same workstation (CPU: AMD Ryzen 3090X with 64 GB memory; GPU: RTX 2080 Ti with 12 GB memory).

Statistical methods

The influence of stepwise strength loss of the VL was determined by linear regression (LR) using the statistical parametric mapping (SPM) package (SPM1D, www.spm1d.org) in Python (www.python.org) with a critical threshold of 5% ($\alpha = 0.05$).[28] The muscle strength of the QUAD (VL, VI, VM, and RF), ILPSO, GLUT, HAM, BIFEMSH, GAS, SOL, and TA, and angle and moment of the hip, knee, and ankle joints were evaluated. The last 30 complete gait cycles of each simulation with a standard duration of 60 s were used for the analysis, and each individual gait cycle was interpolated to 101 data points. Figures were generated using the Python library "matplotlib."[29] The 95% confidence intervals (95% CIs) were calculated by bootstrapping with 1000 replications using the Python library "scipy."[30]

Results

The simulation showed a normal gait for both healthy VL (Video 1) and all levels of VL loss at fast walking speed and for the lower level ($<$50%) of VL loss at self-selected walking speed. During simulation of all these different walking conditions, no falls occurred. The model's preferred speed at "self-selected walking" reached a speed of 1.18 m/s (95% CI 1.15–1.20 m/s) and was within the range of preferred walking speed for healthy adults presented in the literature, which lies between 0.9 and 1.2 m/s.[31] The fast walking speed of 1.62 m/s (95% CI 1.62–1.63 m/s) was just below the maximum walking speed for healthy adults, which has been

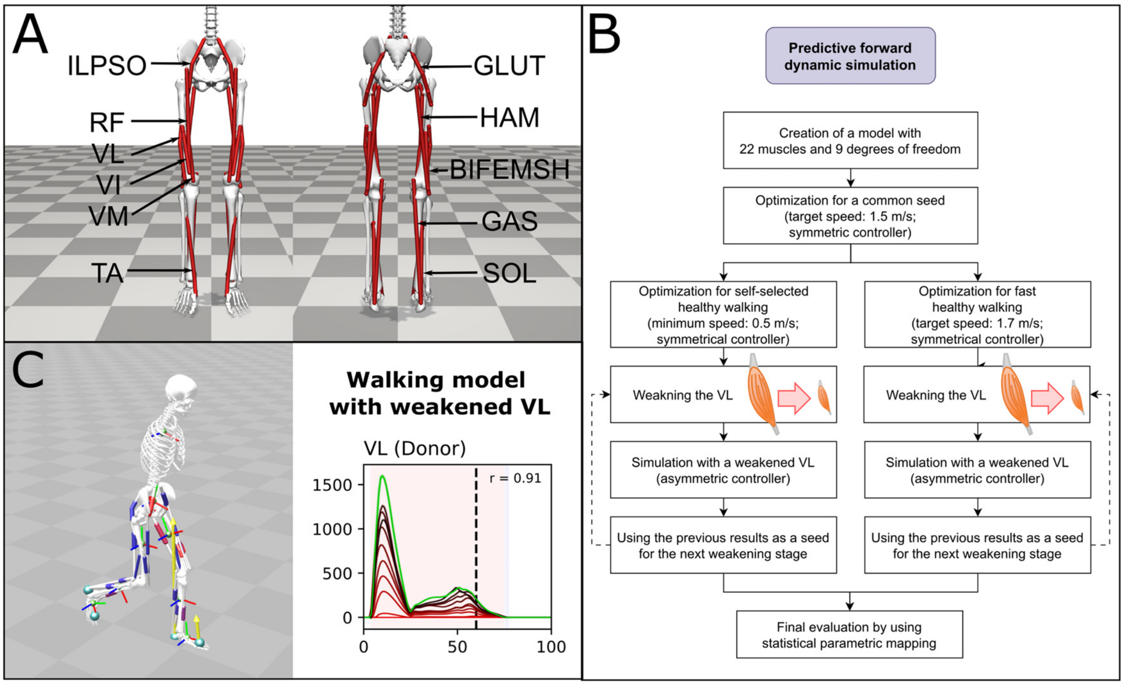

Figure 2 **(A)** Creation of a healthy model with 22 muscles and 9 degrees of freedom: Iliopsoas (ILPSO), vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), rectus femoris (RF), tibialis anterior (TA), gluteus maximus (GLUT), hamstring (HAM), biceps femoris short head (BIFEMSH), gastrocnemius (GAS), and soleus (SOL). **(B)** The main steps of the performed simulation in SCONE explained in a flowchart. **(C)** Left illustration of a walking model with a weakened VL in SCONE. The activation level of the muscles is shown on a color range between blue (nonactivated) and red (activated). White corresponds to the tendons. Contact geometry, body axes and external forces are also shown. On the right, a plot of the evaluation of the VL on the donor site using statistical parametric mapping.

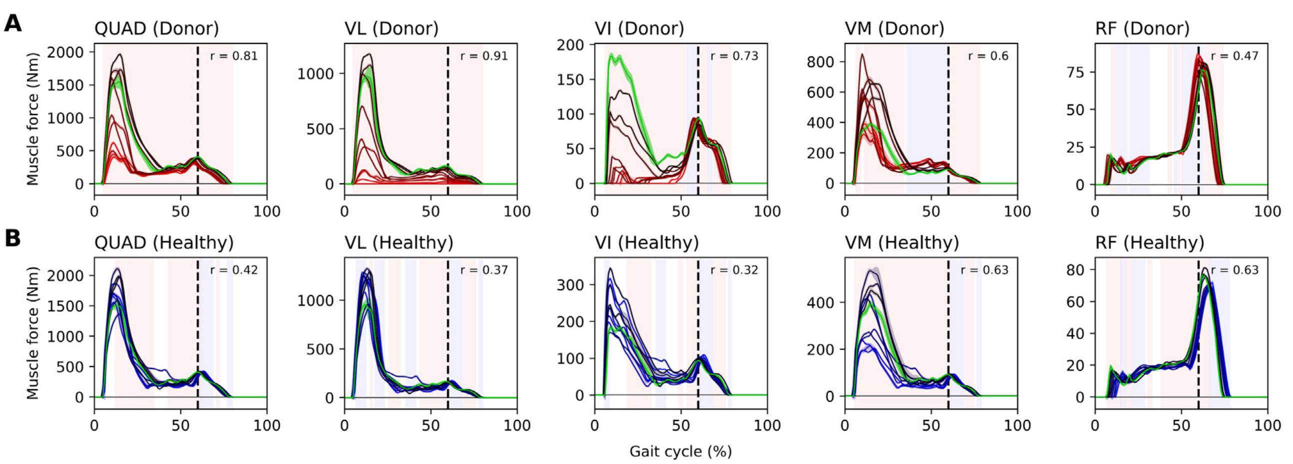

Figure 3 The muscle strength of the quadriceps and its four heads, i.e., vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), and rectus femoris (RF), at self-selected walking speed at the donor site (A) and the healthy site (B). The x-axis shows the gait cycle. The vertical dashed line at 60% shows the split between stance phase (0% - 60%) and swing phase (61% - 100%). The Y-axis shows the muscle force in Nm. The green line shows the muscle force without VL weakening. The gradation of the lines from black to red (at the donor site) or to blue (at the healthy site) corresponds to the gradual functional reduction (100% to 0%) of the VL at the donor leg. The reddish shaded background shows areas of decrease, and the bluish shaded background shows areas of increase according to linear regression evaluated with statistical parametric mapping.

described in the literature as 1.75–2.53 m/s.[32] This is probably because our model is planar, has fewer joints and muscles, and employs a simplified control strategy compared with real-world subjects.

The loss of VL on the donor site (DS) leads to an increasing reduction of QUAD activation at a self-selected walking speed, resulting in an average of less than 616 Nm (≙ 46% reduction) muscle force than those in the healthy side (HS)

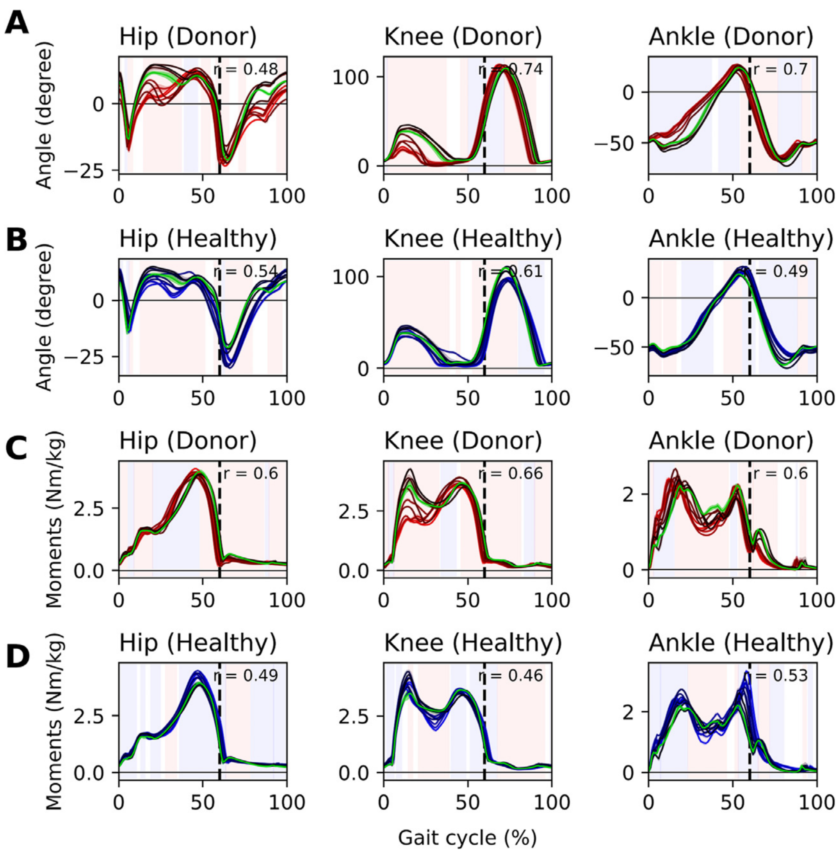

Figure 4 Joint angle and moment during self-selected walking speed at the donor site (A, C) and the healthy site (B, D). **(A, B)** The angle (degree) of hip, knee, and ankle. The X-axis shows the gait cycle. The Y-axis shows the joint angle in degrees. **(B, D)** The join moment of hip, knee, and ankle. The X-axis shows the gait cycle. The vertical dashed line at 60% shows the split between stance phase (0% - 60%) and swing phase (61% - 100%). The Y-axis shows the joint moments (Nm/kg). **(A-D)** The green lines show the joint angle or moment without VL weakening. The gradation of the lines from black to red (at the donor site) or to blue (at the healthy site) corresponds to the gradual functional reduction (100% to 0%) of the VL at the donor leg. The reddish shaded background shows areas of decrease, and the bluish shaded background shows areas of increase according to linear regression evaluated with statistical parametric mapping.

and arises mainly from the reduction of the VI and VL on the DS. On the HS, however, there is a slight increase in QUAD activation, which is again caused by the VI and VM (Figure 3). Therefore, the QUAD activity of the intact leg slightly is aligned to the donor leg. The VI followed the VL reduction at the donor leg in the stance phase. VM activity, on the other hand, was initially increased, then dropped down to the level of the DS. These changes can be interpreted as balancing adaptations to minimize energy expenditure during locomotion and lead to an asymmetry between both legs, which results in limping on the DS starting from a VL weakening beginning at 50% (Video 2). This is additionally indicated by the changed joint motion ranges, especially in the knee and hip joint (Figure 4). Anterior trunk bending was not observed.

During a fast walking speed, the activation reduction of the QUAD was much less pronounced as VI and VM increased clearly in strength. However, from 30% VL weakening, a greater decrease in QUAD muscle strength was observed. Whereas with a 10% VL muscle reduction corresponding to a muscle cuff, this resulted in no relevant change. In contrast to the self-selected walking speed, a weakening of the VL at fast walking speed did not result in balance adaptation because of very high muscle activation, neither was the QUAD weakened to such an extent that a "quadriceps avoidance gait" appeared (Figure 5 and 6) or another obvious pathological gait pattern such as anterior trunk flexion was observed (Video 3). This can also be seen in the corresponding unchanged joint motion ranges (Figure 6).

At both walking speeds, particularly the VM and VI played a prominent role in compensation. In contrast, the RF on the DS, as a biarticular muscle that can additionally flex the hip,[33] had little contribution to these adaptations. This is probably because of its relative weakness compared with the other QUAD heads (Figure 3, Figure 5).

The changes of remaining musculature of the lower extremity (ILPSO, GLUT, GAS, HAM, and BIFEMSH) should be viewed in the context of the adaptations because of altered activation of the QUAD,[16] which showed higher variability at a self-selected walking speed than at a fast walking speed. The SOL and QUAD are activated especially at the beginning of the stance phase, with the SOL developing its force at the

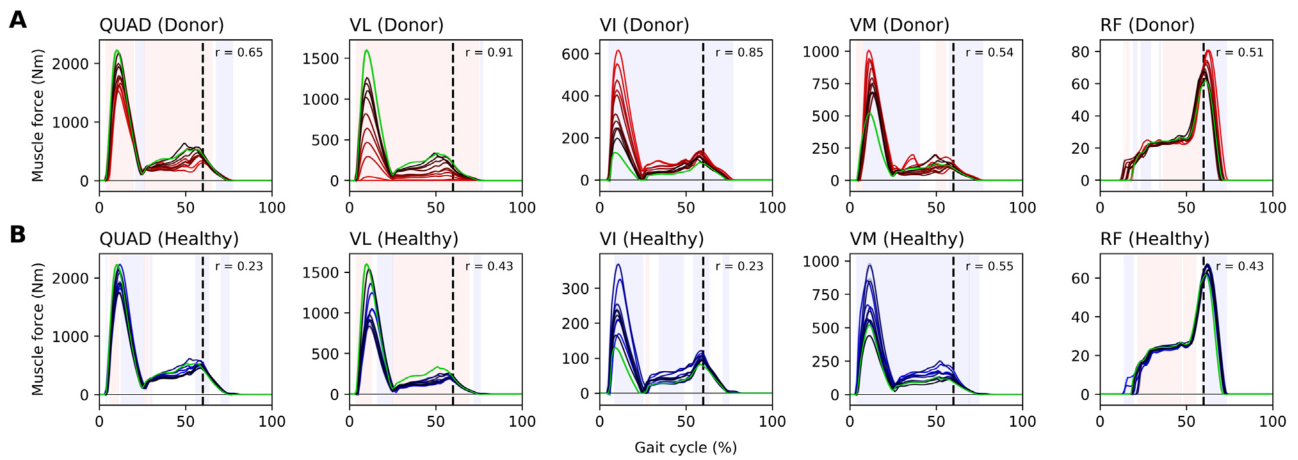

Figure 5 The muscle strength of the quadriceps and its four heads, vastus lateralis (VL), vastus intermedius (VI), vastus medialis (VM), and rectus femoris (RF) at fast walking speed at the donor site **(A)** and the healthy site **(B)**. The x-axis shows the gait cycle. The vertical dashed line at 60% shows the split between stance phase (0% - 60%) and swing phase (61% - 100%). The Y-axis shows the muscle force in Nm. The green lines show the muscle force without VL weakening. The gradation of the lines from black to red (at the donor site) or to blue (at the healthy site) corresponds to the gradual functional reduction (100% to 0%) of the VL at the donor leg. The reddish shaded background shows areas of decrease, and the bluish shaded background shows areas of increase according to linear regression evaluated with statistical parametric mapping.

ankle joint and the QUAD at the knee joint.[16] The change in QUAD resulted in opposite de- or activation of the SOL. The TA showed parallel variability in line with the linked muscle reflex function of the SOL and TA[16] (Supplementary Figure 1 and 2). In general, the adaptations of the other muscles should be considered in the design of the model according to Geyer and Herr, which is closely aligned to the physiological muscle reflex patterns of humans.[16]

Discussion

The VL and myocutaneous ALT flaps are frequently used because of their various advantages.[1-3] Nevertheless, musculoskeletal dysfunction occurs postoperatively in nearly 1 out of 20 patients.[12] It remains unclear at which degree of muscle reduction this problem occurs and whether it could be avoided by adjusting the surgical approach, i.e., less muscle resection by muscle-sparing flap-raising, as recommended by Toia et al..[11] A predictive dynamic forward simulation was, therefore, performed to investigate the effects of flap-raising (i.e., VL muscle reduction) on human locomotion. To do so, we used a mathematical model that produces a realistic human locomotion to get insights into the impact of VL muscle reduction.[15,16]

In this regard, modeling and simulation of the neuromusculoskeletal system can be divided into two different approaches: kinematic and dynamic simulation. The kinematic simulation only describes the motion of a system independent of the causing forces, i.e., it ignores any kind of force change such as due to muscle reduction and thus would not be suitable for this research question. In contrast, dynamic simulation could provide information about muscle forces. It can be further divided into the inverse and the forward dynamic simulation. The first relies on motion data from real patients from which forces are calculated (e.g., muscle and joint reaction forces), while the latter uses mathematical models to simulate forces to generate motion.[14] However, inverse dynamic simulation would only be suitable if muscle force was gradually reduced in the context of experimental surgery. However, this would be unethical. In this context, the use of predictive forward dynamic simulation has many advantages as it allows gradual reduction of muscle force, which cannot be performed in such detail on real patients. The approach is, additionally, very standardized because it does not depend on multiple patient factors such as age, training, and other neuromusculoskeletal conditions, thus without the influence of confounding factors that normally occur in in vivo follow-up studies. Furthermore, it can be repeated at any time while using different parameters.[14,15]

Indeed, the successful use of predictive forward dynamic simulations using the open-source software SCONE has already been demonstrated in predicting gait adaptations because of plantar flexor muscle weakness and contracture in the ankle joint[27] or, more recently, the effect of quadriceps contracture.[34] The results of those simulations were very realistic and confirmed by observations on patients,[27,34] suggesting the utility of such models.

The results of our study showed different compensation mechanisms depending on the walking speed (self-selected vs. fast), the muscle, the affected leg, and the degree of muscle reduction. At self-selected walking speeds, the reduction of the VL muscle could only be partially compensated with the reduction of QUAD activity (Figure 3) and led to limping at VL reductions of 50% and more (Video 2). This resembled the first strategy of a "quadriceps avoidance gait" as observed in patients after anterior cruciate ligament defects[35,36] or with patellofemoral pain,[37] in which the knee flexion angle is decreased in mid-stance to reduce the load on the QUAD.[35,36] This is particularly relevant in elderly or fragile patients with limited mobility, who usually cannot or do not walk fast anymore. The second strategy would be to

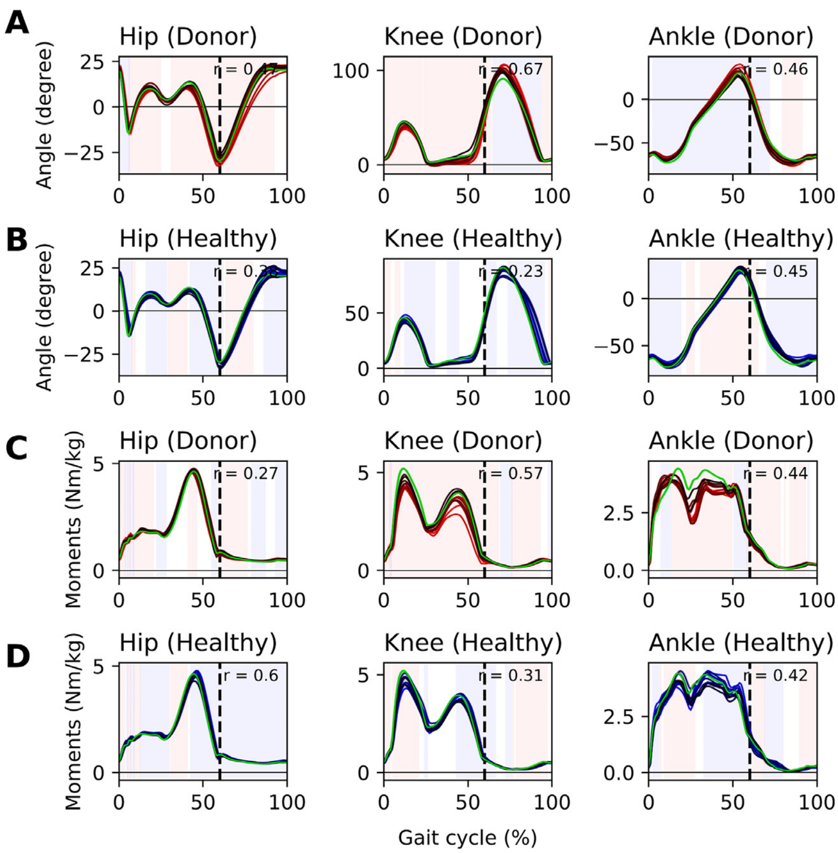

Figure 6 Joint angle and moment during fast walking speed at the donor site (A, C) and the healthy site (B, D). **(A, B)** The angle (degree) of hip, knee, and ankle. The X-axis shows the gait cycle. The Y-axis shows the joint angle in degrees. **(B, D)** The join moment of hip, knee, and ankle. The X-axis shows the gait cycle. The vertical dashed line at 60% shows the split between stance phase (0% - 60%) and swing phase (61% - 100%). The Y-axis shows the joint moments (Nm/kg). **(A-D)** The green lines show the joint angle or moment without VL weakening. The gradation of the lines from black to red (at the donor site) or to blue (at the healthy site) corresponds to the gradual functional reduction (100% to 0%) of the VL at the donor leg. The reddish shaded background shows areas of decrease, and the bluish shaded background shows areas of increase according to linear regression evaluated with statistical parametric mapping.

lean forward in mid-stance while maintaining a normal knee flexion angle,[35] which was not observed in our model, probably because sufficient QUAD functionality from intact VI and VM was still possible. In contrast, gait disturbances such as limping did not occur during fast walking speed. Yet, a considerable decrease in QUAD muscle strength was observed starting at 30% VL weakening.

However, what is the clinical implication that can be drawn from these results? As previously mentioned, on average, the three partitions of the VL account for 42.6% of the superficial (95% CI 37.9–47.0%; calculated by 1000-repeated bootstrap), 33.9% of the intermediate (95% CI 31.3–35.7%), and 23.5% of the deep partition (95% CI 17.4–28.3%).[11] In this regard, flap-raising only of the superficial partition of the VL would correspond to a muscle reduction of under 50%. Therefore, our results suggest that in elderly and fragile patients, limiting the flap-raising to this partition might help prevent musculoskeletal dysfunction. Considering that the superficial part (≙ 42.6%) of the VL already accounts for more than 30% of the muscle mass, raising the superficial partition in young or athletic patients would lead to a decrease in athletic performance. One option would be to only raise the deep partition of the VL, but this is not recommended according to Toia et al. because it is important for lateral stability of the patella.[11] Therefore, in young or athletic patients with the need for a larger amount of muscle in the flap design, switching to other established flaps such as the latissimus dorsi would be an option. In contrast, a pure muscle cuff (≙ 10%) seems to be tolerable.

In addition to muscle reduction itself, VL function may be impaired by motor nerve damage.[38] This is of high clinical relevance because accidental nerve dissection proximal to the muscle and without reconstruction would result in permanent 100% failure, as also specified in the model. Damage after the separation of the nerve into the individual partitions would only lead to a complete failure of the affected partition.[11] Therefore, care should be taken to preserve the neural supply to the nonraised partitions in order not to exacerbate a possible negative effect on locomotion. In case of accidental dissection of the nerves, these should be pri-

Table 1 Change in muscle activity depending on walking speed.

Walking Speed		Self-selected		Fast	
Site		Donor	Healthy	Donor	Healthy
Muscle force (Nm)	QUAD	↓	↑	↓	↓
	VL	↓	↑	↓	↓
	VI	↓	↑	↑	↑
	VM	↑/ø	↑/↓	↑	↑
	RF	ø	ø	↑	ø
	ILPSO	ø	↑	ø	ø
	GLUT	↑	↑	↑	↑
	HAM	↓	↑	↓	↓
	BIFEMSH	↓	ø/↓	ø	↑
	GAS	↑	ø	↑/↓	ø
	SOL	↓	↑	↓/↑	↑
	TA	ø	↑	ø	↑
Angle (degree)	Hip	↓	↓	ø	ø
	Knee	↓	ø	ø	ø
	Ankle	↓	ø	ø	ø
Moments (Nm/kg)	Hip	↑	↑	ø	ø
	Knee	↓	↑	↓	↓
	Ankle	ø	↑	↓	↓

↑ = increase; ↓ = decrease; ø = no change; changes at the beginning/later; BIFEMSH: biceps femoris short head; GAS: gastrocnemius; GLUT: gluteus maximus; HAM: hamstrings; ILPSO: iliopsoas; QUAD: quadriceps; RF: rectus femoris; SOL: soleus; TA: tibialis anterior; VI: vastus intermedius; VL: vastus lateralis; VM: vastus medialis.

marily reconstructed with the aim of enabling recovery of muscle strength.[39]

It should be noted that neuronal remodeling[40] and obesity[41] were not accounted for in our model, leading to variability in the aforementioned cutoff values. Also, insights into the role of individual muscles might guide targeted instead of generalized physiotherapy to mitigate musculoskeletal dysfunction, particularly in these patient groups (Table 1).

However, the possible occurrence of pronounced scarring after flap-raising with possible influence on locomotion was not addressed. Scars lead to a restriction of movement and not to muscle weakness and are not primarily dependent on the amount of muscle mass taken, but on other factors.[42] For example, the degree of deep fascia damage has been discussed as a cause of musculoskeletal dysfunction.[12] Nevertheless, pathological scarring is rare[42] among other reasons probably because of early mobilization.

Conclusion

Our simulation showed several aspects. VL muscle reduction could be generally compensated up to a certain degree, which could explain the observed incidence of musculoskeletal dysfunction. In elderly or fragile patients, the VL muscle should not be reduced by 50% or more, which could be achieved, for example, by muscle-sparing harvesting of the superficial partition. In young or athletic patients, the 10% VL muscle reduction, which corresponds to a muscle cuff, has no effect, but significant weakening of the quadriceps can occur beginning at 30%. Therefore, in this patient population with the need for a large portion of muscle, alternative flaps could be considered. Furthermore, the nerve supply of the nonraised partitions of the VL should be respected in order not to exacerbate a possible negative effect on locomotion. This study can serve as the first basis for further investigations of human locomotion after flap-raising.

Author contributions

Conceptualization, B.P., A.M., and F.H.; methodology, B.P. and T.G.; software, B.P. and T.G.; validation, B.P., U.T. and K.S.H.; formal analysis, B.P., M.O., I.M., A.R., F.H., and A.M.; investigation, B.P. and L.G.; resources, B.P. and F.H.; writing—original draft preparation, B.P; writing—review and editing, B.P., A.M., M.O., T.G., U.T., K.S.H., L.G., I.M., A.R., and F.H.; visualization, B.P., M.O., and A.R.; supervision, F.H. and U.T.; project administration, B.P.

Funding

This research received no external funding.

Institutional review board statement

Not applicable.

Informed consent statement

Not applicable.

Data availability statement

The data presented in this study are available upon request from the corresponding author.

Declaration of Competing Interest

Thomas Geijtenbeek is the creator and proprietor of the Hyfydy simulation software, which has been used in this study to speed up the optimizations. The other authors declare that they have no conflict of interest regarding the results and methods published in this article.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.10.036.

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