Matching a specific patient with an optimal treatment for their walking limitations remains challenging. In this thesis, the feasibility and validity of the motorized resistance test and interactive gait lab were examined to clinically assess motor (dys)function in children with CP in order to inform clinical decision making.

First, the ability of the motorized hyper-resistance test to identify neuromuscular characteristics of the calf muscles was examined as a standardized alternative to the manual tests performed during physical examination. For this purpose, a measurement protocol was developed based on a motorized ankle manipulator combined with an adjustable chair and foot fixation. A non-linear neuromuscular ankle model was extended and adjusted to CP children. The applicability of the motorized test was examined by testing in a relatively large and heterogeneous population of CP children as well as their peers and by comparison to current clinical outcomes and instrumented manual testing. Second, to examine the use of the interactive gait lab to assess gait abnormalities, several fundamental studies compared the interactive gait lab with conventional treadmill walking and traditional overground clinical gait analysis. This included a thorough examination of the technical performance of the instrumented treadmill as well as its interaction with a subject. The applicability of the interactive gait lab was examined by measurements in typically developing children and children with CP.

Third, the first step was taken to integrate hyper-resistance testing in clinical gait analysis, for functional reflex assessment during gait. A protocol with different types and intensities of perturbations was developed to study whether mechanical perturbations could evoke muscle responses, using musculoskeletal modelling to examine the stretch reflexes.
The general discussion starts with a reflection on the general feasibility and validity of the motorized hyper-resistance test, interactive gait lab and functional hyper-resistance test by combining the evidence provided in the different chapters. In addition, an outlook is given on potential future research. The second part zooms in on a major challenge that underlies all these diagnostic tests, which is to find a compromise between complexity of the measurement and analysis to make the outcomes reflect physiological characteristics of the neuromuscular system as much as possible, versus the interpretability and clinical relevance of the outcomes. This discussion also relates to the next topic, which is the practical and strategic issues related to clinical implementation of the tests. And even after implementation technological development is never finished, thus directions are given in the fourth part to further increase the added value of the tests for clinical decision making. Finally, an overview is given of the direct clinical implications of the work presented in this thesis.

**Feasibility and validity**

To address the aim of this thesis, the feasibility and validity of the different tests are discussed below, as well as some directions for future research.

*Motorized hyper-resistance test*

The motorized hyper-resistance test was introduced as a standardized alternative for current clinical manual tests, and allowed for quantification of the muscle response and modelling of the underlying neural and tissue related causes. All included patients could be measured within approximately 30 minutes (chapter 2). This cannot be generalized without a doubt to other patients within the target population. For instance, the test’s applicability might be lower in patients with CP and younger than 6 years because of a generally lower ability for younger children to relax. The same argument holds for more severe patients of GMFCS level 3 and higher, although the hyper-resistance of the ankle might be of less clinical interest for these patients. Thus, it can be concluded that the hyper-resistance test was feasible for children with CP with GMFCS I and II of 6 years and older.

The construct validity of the hyper-resistance test was demonstrated at different levels (chapter 2). First, at the level of internal model validity, it was demonstrated that all model parameters were required and together well able to describe the measured data. Second, with regard to precision, the measurements showed a moderate to good repeatability. Third, at the level of external model validity, the outcomes were corresponding with current knowledge of muscle physiology and could discriminate between the CP population and their peers according to CP pathology. In addition, background muscle activity was found to be sensitive to clinically assessed spasticity severity, with a similar trend for reflex activity. This weaker relation of reflex activity could be related to the dissimilar response to passive stretch between motorized and manual tests (chapter 3). The differences between methods found in the movement profile, including the magnitude and profile of acceleration, implicate that the motorized hyper-resistance test cannot be used interchangeably with current clinical manual
Discussion

tests. Finally, preliminary data indicated that reflex activity was sensitive to spasticity treatment. Together, these results suggest that the quantified neuromuscular characteristics seem a valid representation of the neuromechanics of CP pathology.

Unfortunately, a “gold standard” method does not exist to validate our individual test results. An alternative would be to validate the physiological principles of the neuromuscular model using animal studies, e.g. measuring muscle stiffness and reflex activity of spastic rats in vivo and in a controlled way. The central neuronal circuitries of humans rest on the same principles as animals, however, there are some considerable differences, including a greater dependency on supraspinal control of movement. These differences warrant further experimental validation of the hyper-resistance tests in human subjects. This includes the evaluation of a few basic assumptions that still need be justified, such as the notion that muscle length change is linearly related to ankle rotation; that the foot fixation minimizes any foot deformation affecting this relation; and that the contribution of the tendon compliance is negligible. Recent studies using ultrasound found a reduced muscle belly lengthening with ankle rotation and an increased effect of the tendon elasticity for children with CP compared with TD. As for the foot fixation, its mechanism has been suggested to be effective in limiting but not eliminating foot deformation in a child with CP based on X-ray data. However, this should be confirmed in more patients at larger ankle angles (or higher torques), comparing different types of foot fixation using for instance CT-scans. In addition, the assumption of relaxation (i.e. no muscle contraction) deserves more investigation. To evaluate the quality of a measurement and thus the outcomes, it should be established which levels of activation are still acceptable based on objective criteria.

Next to model validation, evidence of the clinical usefulness of the outcomes should be further established. The large variance between patients in the ratio of stiffness versus neural related resistance indicates that the method could potentially contribute to patient-specific treatment selection. Nonetheless, this should be solidified by large patient studies establishing the sensitivity of the outcomes to different treatments that target different impairments, i.e. botulinum toxin injections, selective dorsal rhizotomy and intrathecal Baclofen therapy versus passive stretching and casting. In addition, to fully exploit the quantitative data, the ability to match patients and predict functional treatment outcomes should be explored. Lastly, to gain a better understanding of the relation between motorized and manual spasticity assessments, the effect of different movement profiles should be further examined. Moreover, even though current clinical tests do not assume to replicate functional movement, the representativeness of the outcomes to motor performance during for instance gait could be increased by further adjusting the imposed movement to (individualized) stretches during gait and thus develop iso-functional profiles. Answers to all these research questions will contribute to the development of instrumented spasticity assessment protocols that will improve treatment planning and outcome evaluation in patients with spasticity.
**Interactive gait lab**

The interactive gait lab was introduced as an improved alternative to conventional treadmill walking and overground gait analysis. There exists some controversy whether instrumented treadmills are able to correctly measure ground reaction forces during gait. It has recently been theoretically demonstrated that the forces exerted by a subject on a moving treadmill belt are accurately transmitted to the force sensors. Nevertheless, this simple model did not include mechanical vibrations, treadmill belt elasticity, or resonance of the structure. Therefore, a protocol was presented for instrumented treadmills to support the measurement of potential sources of systematic error, and also to facilitate comparison amongst literature. According to this protocol, it was verified that the interactive gait lab showed satisfactory results for most technical requirements for gait analysis (Chapter 4). This included the force sensor characteristics (linearity, hysteresis, crosstalk and drift), while the system resonance was shown to be outside the range of interest for gait and above common low-pass filter frequencies. In addition, the belt speed did vary a little at heel strike and toe-off, but the resulting interactions between treadmill and subject were found to have at most a mild effect on the gait pattern (Chapter 7). The mechanical noise was less optimal, but its effect can largely be averaged away over multiple strides that can be easily measured with a treadmill. Force and center of pressure accuracy was in line with most treadmills, and could be further improved by calibrating specifically within the actual walking area (Chapter 5). Nevertheless, errors of this magnitude have been shown to slightly affect gait measures so caution is warranted with interpretation of joint moments in especially the frontal plane. Unfortunately, the representativeness of static accuracy measurements for the actual accuracy during gait is unknown. One of the error sources potentially lowering force accuracy during gait are inertial artefacts, caused by accelerations of the belt. These artefacts can especially have an effect when acceleration perturbations are applied, fortunately a compensation algorithm has been presented. To examine the accuracy under experimental conditions functional tests should be performed on a running belt, i.e. dynamic calibration. Finally, to truly determine the extent to which a treadmill is a technically valid tool to examine gait, it is imperative to know the effect of different error sources on the interpretation of clinical gait analysis. Overall, the instrumented treadmill, if used and calibrated properly, seems adequate for standard (clinical) gait analysis.

All included subjects, i.e. healthy adults, typically developing children (8 to 15 years), as well as ambulant children with CP (8 to 14 years; GMFCS I and II), were able to walk in the interactive gait lab after habituation. The feasibility still has to be determined for younger children, especially those with CP, as well as for more severe patients. Both groups might have more problems with controlling the self-paced algorithm or dealing with the visual flow without losing attention.

The self-paced (SP) and virtual reality (VR) environment of the interactive gait lab did not or negligibly affect the gait pattern of healthy adults, children and children with CP, compared with fixed speed walking and walking without a VR (Chapter 6-9). This demonstrates that the different modes can be used interchangeably for
gait analysis. The reliability of gait parameters, especially in SP condition, has not been examined yet. However, a consistent average walking speed was obtained for healthy adults using another feedback-controlled treadmill \cite{12}. The interactive gait lab was more representative of overground walking than conventional treadmill walking, with a more realistic environment provided by the VR. In addition, self-paced walking resulted generally in more low-frequency fluctuations in SP walking speed that seemed to correspond with larger fluctuations seen during normal overground walking \cite{13-15}, although this comparison still has to be made directly. Small differences between walking with or without a VR suggest that awareness of the position on the treadmill could be important. It seemed that some children might need more time to familiarize to the treadmill-walking, although the use of VR has been shown to reduce the required habituation time \cite{16}.

Typically developing children and children with CP walked somewhat differently in the interactive gait lab compared with the overground lab (Chapter 10 & 11). This does not only include wider step width, which is typical for a split-belt \cite{17}, but also a shift was found from an ankle to a hip strategy for generating work. The reduction in ankle push-off power has also been reported for healthy adults and elderly \cite{18,19}, and was in line with other treadmill to overground comparisons made in children\cite{21,22}. This stresses the need for sufficient habituation time on the treadmill especially in children. The fact that overground walking and in the interactive gait lab cannot be readily compared, does not mean that the interactive gait lab analysis is not valid for assessing gait aberrancies in a context of clinical gait analysis. Both labs are controlled conditions, and as such, both have been found to differ from unrestricted free overground walking. The question remains which controlled situation is most relevant for clinical evaluation of walking performance. First, patients seem to walk more in their pathological gait patterns in the interactive lab, with for instance more knee flexion at initial contact. This could be due to a lower awareness of the present examiner, distraction by the VR environment, higher attentional demands necessary for the control of the SP walking, or increased energetic demand and longer walking time resulting in more fatigue. Second, children with CP preferred the interactive gait lab, thus demonstrating that it provides a more motivating environment. The question remains how children with impaired processing of visual information respond to the VR environment, although the environment can also be intentionally used to examine how these children walk in busy environments. Lastly, the interactive gait lab provides means to challenge patients outside their normal walking pattern, to measure more consecutive strides and the effect of fatigue. This suggests that the interactive gait lab might even be a more useful clinical tool than a conventional overground gait lab.

Several steps can be taken to further broaden the understanding of the effect of SP treadmill walking and a VR environment. Since children walk more differently on a treadmill compared to adults, the effect of different SP control mechanisms should be examined in children and in patients specifically, as these might be differently optimized for these groups. The different effects of VR environment reported in literature raises the question how different scenes as well as variation in the speed
of the optical flow affect the gait pattern and attention of children and patients. In addition, for feedback applications it would be informative to follow the actual gaze using techniques such as eye tracking, in order to present the feedback in the field of view and not interfere with normal gazing during gait.

In conclusion, the interactive gait lab is technically adequate for gait analysis, feasible in older and less severe children with CP, provides a more realistic environment compared with conventional treadmill walking and forms a promising alternative to overground labs, although their results cannot be readily compared.

**Functional hyper-resistance test**

To identify neural impairments during gait, the ability of treadmill belt accelerations to evoke stretch reflexes has been examined. The perturbations could be applied to healthy adults without causing falls or affecting the general walking pattern, demonstrating its general feasibility (Chapter 12). However, the effect of the perturbations on the able-bodied adults cannot be automatically generalized to all spastic patients, but most likely depends on the gait pattern of a specific patient, especially the angle at mid stance when the perturbation is applied. In addition, the effect on the walking pattern of spastic patients might be larger, for some have problems with stability during gait and others might become more frightened during the perturbations, possibly resulting in an anticipatory change in muscle activation.

The use of anterior-posterior accelerations or decelerations to perturb gait has only been used in few studies to date. Most of them used perturbations to replicate a trip or slip to study balance and gait adaptability, although also continuous sinusoidal perturbations have been applied. The intensity of these perturbations, i.e. maximum acceleration or deceleration, were lower (2 ms⁻²; cerebellar patients) slightly higher (5-6 ms⁻²; elderly) and significantly higher (over 20 ms⁻²; lower limb amputees) than those used in our study. In most of these studies, subjects were able to maintain their balance, but made adaptive changes to their gait, with the exception of the high-intensity perturbations that resulted in some falls. Treadmill perturbations have been used in the eighties to evoke stretch reflexes in a limited set of subjects with mild spasticity, i.e. fifteen spastic adults, two children with mild spastic CP (7 and 13 yrs), and 30 typically developing children (1-8 yrs). However, specifics of their gait pattern were not reported, nor any potential anticipatory or anxiety effect. Another study evoked stretch reflexes using high-intensity perturbations applied with a mechanical ankle joint in children with (GMFCS I and II, including toe-walkers) and without CP (4 to 14 yrs old). They reported that after some familiarization, all children felt comfortable with the perturbations and walked relaxed, although the ability of the mechanical joint to evoke stretch reflexes in toe-walkers might not be representative for belt perturbations. Together, these studies suggest that the mild perturbations applied in the functional hyper-resistance test should be feasible in children with CP. Future research should further elaborate on the effect of the perturbations on patients, especially those that exhibit an abnormal gait pattern such as toe walking or crouch gait.
Our findings demonstrated that the accelerations were able to elicit long latency stretch reflexes in the major calf muscles and tibialis anterior of healthy adults. Not all subjects responded to the highest intensity, suggesting that a higher intensity should be added to the protocol. On the other hand, stretch reflex thresholds are expected to be lowered in spastic patients\(^\text{33,34}\). Further validation should be based on more instantaneous perturbations that allow for a better determination of the reflex delay and thus distinction between short and long latencies. In addition, to validate the representativeness of muscle tendon unit velocity and assumed absent role of the Achilles tendon’s compliance, muscle fascicle length change should be directly measured with ultrasound during perturbations. For the soleus muscle, it has already been shown that the muscle fascicles follow the changes in ankle angle induced by a mechanical joint\(^\text{35}\). Using these data, a clinical meaningful and robust quantification of the reflex response should be established, for instance based on the principle of the response strength or dynamic spasticity. It should be noted that these measures are only based on stretch velocity, while the muscle response is a complex, non-linear function of force, muscle length and velocity as well as gait phase. To aid clinical interpretation, the clinical measure should be compared to current clinical spasticity tests as well as motorized and/or manual instrumented assessment, even though these are performed under passive conditions\(^\text{36,37}\). In addition, the relation with other experimental dynamic measurements would be interesting to examine, including measurements with the mechanical joint or with manipulated walking velocity\(^\text{32,33}\). Overall, the presented work encourages further examination of treadmill perturbations for functional assessment of hyperreflexia during treadmill-based clinical gait analysis in spastic patients.

**Complexity vs. interpretability**

A major challenge for designing diagnostic tests is to find a compromise between model complexity and interpretability, or clinical relevance, of the outcome measures. On one hand, scientists and engineers tend to strive for measurements that produce increasing amounts of information, to feed models which are the most optimal representation of the underlying neuromuscular system. However, increasing complexity of measurements and information make the outcomes less accessible and more difficult to relate to clinical problems. In addition, expanded model complexity comes at the risk of interdependence of model parameters.

The different levels of complexity of clinical gait analysis show a trend of acquiring increasing amounts of data and outcome parameters (Fig. 13-1). The most simple analysis is based on observation of the gait pattern while the patients walks for instance through the hallway. However, this assessment by the physician is not quantitative and cannot be reviewed. This is tackled by video registration, which allows for offline assessment of the gait pattern from different perspectives, and specific phases of the stride cycle, image by image, using digital goniometric tools to measure joint angles. The next step in objective gait analysis are technologies that combine simple motion registration systems with sophisticated image analysis to automatically derive
kinematics from video recordings. Next to the registration of body movement, ground reaction forces and muscle activity are often registered simultaneously using ground-mounted force plates and EMG. This can also be combined with 3D gait analysis, relying on more advanced optoelectronic tracking of markers attached to the body. Up to this level, increasingly advanced technology is used to observe the normal gait pattern without interfering. To learn more about the underlying characteristics that hinder walking, the response to perturbations applied during normal gait is examined. For instance, different types of perturbations have been used to measure gait stability, the modulation of mechanical ankle properties, motor control, or stretch hyperreflexia as shown in this thesis (Chapter 12). Instead of passive perturbations, the patient’s gait pattern can also be examined by challenging a patient out of his or her normal walking pattern by continuously adjusting a given task, for instance by using visual feedback. While these measurements are usually performed in the gait lab, different measurement systems of increasing complexity are also becoming available to study movement during daily life, for instance using inertial sensors to measure gait stability and 3D kinematics.

Similarly, the development of spasticity tests also shows a trend from simple to more complex tests (Fig. 13-2). The (modified) Ashworth scale was introduced to rate spasticity, or technically the resistance to fast passive stretch. Alternatively, the pendulum test has been used to quantify the muscle response to fast drop of the leg using tachometers, with increased reflex activity or viscoelasticity damping the swinging of the leg. Although not instrumented, the (modified) Tardieu scale included different stretch velocities into their measurement to account for the velocity component. It consists of rating the muscle response to fast stretch and quantified the dynamic component as the difference between the range of motion measured during slow and fast stretch using goniometry. A simplified alternative with standardized stretch velocities was introduced as the spasticity test (SPAT).

To provide more insight into the muscle response to stretch, instrumented versions of the modified Tardieu test have been introduced that include measurement of the imposed movement and the muscle activity (EMG). Outcomes typically include the range of motion and angle of catch. While more parameters can be extracted from the available data, such as based on torque or muscle activity data, the challenge is to extract clinically meaningful parameters. Although quantified observations positively contributed to more standardized classification of patients, neuromuscular modeling was subsequently introduced to disentangle the underlying neural and tissue-related causes of hyper-resistance to stretch. The basis of these models are...
generally formed by the Hill-type muscle model, using muscle characteristics based on normative values. Different choices can be made to fit to a patient's pathology. For instance, increased muscle stiffness can be modeled by changing the shape factor of the passive force-length relationship or shortening of the muscle by a shift in the muscle's slack length or maximal isometric force. Whereas the model used in this thesis estimated increased reflex activity by fitting the data to standard activation and contraction models, it has been shown that a spasticity model can more precisely describe a patient's altered reflex modulation and stretch initiated bursts. Moreover, more advanced system identification and parameter estimation techniques are being developed, such as linear parameter varying subspace identification methods that have been used to model time-varying passive muscle properties over a large range of motion and varying muscle activation, using small, continuous perturbations.

To improve the representation of the (patho)physiology of patients with CP, different model parameters could be added and personalized to quantify the different impairments (Fig. 13-3). In order to try to discriminate between shortening and passive tissue stiffness, the slack length could be estimated from the shape factor of the passive force-length relationship. In case of muscle activation, the active optimal muscle length that plays a role in the contraction dynamics could also be estimated. In addition to muscle tissue stiffness and shortening, passive resistance can be further disentangled by distinguishing intrinsic stiffness and tendon-related compliance, since these are suggested to be of more influence in spastic patients. Most studies use normal values measured in able-bodied adults for the not optimized Hill-type muscle properties. However, these properties are most likely different in spastic patients, as well as in typically developing children. Thus, establishment of normative values for different phenotypes and age- or weight-related scaling of these parameters might considerably improve the models to predict muscle function in individuals. The active component of the model could also be further refined by description of clonus and by improving the distinction between reflex and background activity. Next to stretch reflexes, length- and force dependent feedback could be separately modelled, with varying contributions per muscle. Moreover, even though the task was to relax, influence of central drive on (in)voluntary activation and reflex modulation cannot be excluded, while the force produced by muscle activation might be affected by weakness and atrophy. Lastly, the effects of contraction of the calf muscle are generally regarded as independent, whereas they have been reported to have both mechanical and reflexive interconnections, although their contribution are unknown in spastic patients.

Fig. 13-2. Development of hyper-resistance tests
The increasing amount of information and model expansions come with what could be the disadvantage of more outcome parameters. This can result in interdependency amongst these parameters, a solution to which would be to design experiments that yield enough information to uniquely identify the behavior of the different parameters. This could, however, increase measurement time and thus reduce potential clinical application. Perhaps most importantly, an increasing amount of outcome parameters can be more difficult to interpret and relate to clinical symptoms. More information does not automatically point towards a specific indication for treatment, whereas simple models using a single rating of hyper-resistance or observation of the gait pattern are attractive to clinicians because they seem easy to interpret (although their actual relation with underlying impairments may not be as clear). Therefore, it is important that increasing measurement complexity and model development should be guided by clinical demand, yielding a complexity that is justified by the application. For instance, when complex multi-level surgeries are considered, more advanced gait analysis is justified to obtain detailed information on deviations of the gait pattern. With regard to the discussed model development, a distinction between muscle shortage and stiffness might be of direct consequence for proposed treatment selection: for instance surgical tendon lengthening versus casting or stretching. In addition, the inclusion of soleus and gastrocnemius parameters in our model could theoretically allow for a separation between their contribution, which would be informative for Botulinum NeuroToxin-A treatment planning.

Thus, measurement and model complexity should match the clinical demand. However, more complex measurements and extended models could serve a more scientific exploratory goal, contributing to patient care by increasing our understanding of phenomena such as spasticity. Thus, measurements and analysis should be made as simple as possible, but not simpler.
Clinical implementation

The challenge with clinical implementation, is to establish the inherent value of the technology and the ability to put it to work efficiently. For this purpose, it is important to have a clear view on the intended application(s) of the technology, because tests can contribute in different ways to clinical decision making. For instance, the primary goal of a test can be to characterize impairments in an individual patient using physiologically sound parameters. It can also be to suggest a treatment plan based on less interpretable parameters that can predict treatment outcome, or to contribute to patient-tailored treatments by an increased understanding of how a treatment affects a patient. While these may seem related, the primary purpose of a test determines the required measurement and outcome complexity, target group and required clinical evidence.

In order to enable clinical implementation of new technologies such as motorized hyper-resistance tests, the interactive gait lab, or the functional hyper-resistance test, both practical and strategic issues need to be addressed. Practical issues include the transformation from more experimental set-ups to a practical, easy to perform clinical tests. This holds especially for the hyper-resistance test, which would benefit from validation of the test using a more standard chair and simple to use foot fixation that is applicable to all shoe sizes and comply with bony deformations. In addition, standardized clinical protocols should be developed and normative data sets measured accordingly. For the hyper-resistance test, such as protocol should include an easy tuning of the foot fixation, online EMG check and feedback on the relaxation of a subject, and the option to adjust the movement speed for anxious children. For the interactive gait lab, the protocol should start with familiarization and practice time, to select the children that are able to walk in the interactive gait lab. Those children that walk with a gait pattern similar to previous analysis or daily life according to the parents, could then be further prepared for the measurements. This gives the children some time to rest and habituate to the markers while walking overground before they start the treadmill measurement. For the functional hyper-resistance test, the protocol development should focus on selecting the necessary number of perturbations and repetitions as well as the required difference in intensity for a specific patient group. In addition, the effect on the measurements when holding a handrail or assisting device as well as wearing orthotics should be established.

Next to these practical considerations, four strategic aspects seem essential for successful clinical implementation of the methods: finding early adopters, establishing clinical value, providing education about good use and finding financial aid. For wide-spread clinical implementation, it is important that a test is be adopted from the inventors by early adopters. These early adopters are usually a small group of clinicians with an interest in scientific research who believe in the added value of the test. This group of clinicians is both responsible for further development of the technology as well as its implementation. Consensus meetings, prototype presentations and Delphi rounds can be held to involve the early adopters and steer the development of the tests as well as clinically useful outcome reports. A challenge with this phase,
is that the early adopters might be interested in advanced measurements with accessible data, whereas the majority of the intended users may require a more straightforward outcome report. While the passive and functional hyper-resistance tests are still being developed and validated, the interactive gait lab is already in or beyond this phase. When the early adopters are subsequently willing to adopt the test both in clinical practice and research, an early majority gets exposed to the test by conferences, booths, medical and research papers. The involvement of the early majority can be supported by user groups and (scientific) collaborations. As soon as the clinical usefulness of a test and its outcome measures is established, the large majority (and finally the laggards) will follow.

Together, the early adopters and early majority play an important role in establishing the clinical usefulness of the test and outcome measures. This includes setting up large patient studies of different populations, creating normative and patient databases, examining the sensitivity to different interventions and establishing the clinical value relative to existing clinical tests. Moreover, it should be established how the tests can and do make a difference in treatment decision making. Both the hyper-resistance test and interactive gait lab have only been examined in few patient populations, i.e. CP and stroke as well as CP and transtibial amputees, respectively. Compared with the manual instrumented tests that are currently at the early adopter phase, the hyper-resistance is limited to the ankle joint, but can apply specific controlled perturbations and be used for functional tasks. The surplus value of these advantages for patient characterization and treatment evaluation have yet to be established. The interactive gait lab has some practical advantages over a conventional overground lab, but the added value of the SP walking for fatiguing or stride variability examination and VR for providing feedback is to be examined.

Once the (added) clinical value is established, the next crucial step is to educate users on good use of the test and correct interpretation of its outcomes, starting with their subjection to the particular test. For the interpretation of interactive gait analysis, it is primarily important to recognize typical changes in gait pattern between overground and treadmill walking. For the (functional) hyper-resistance tests, users should learn how the outcomes relate to their own physical examination. In addition, it is important that users know how the performance of the different tests, such as the level of relaxation or cooperation during gait analysis, affects the outcomes and thus their interpretation.

Finally, centers should have financial funding for implementation of a test. Initially, scientific and innovation funds can aid the purchase of the tests to perform large patient studies. For actual clinical implementation, the cost efficiency of these tests, i.e. whether the potentially higher costs of these advanced tests compared with current clinical alternatives are outweighed by their added clinical value, has to be established by the early adopters and majority. If satisfactory, there can be a role for health insurance companies to provide further funding, as standardized quantitative measurements could potentially significantly contribute to evaluation of the necessity of (costly) interventions and avoidance of unnecessary treatment.
Future precision diagnostics

Both the hyper-resistance test as well as the interactive gait lab have many opportunities to further enhance their added value for clinical decision making. In Fig. 13-4, a similar overview of the examination and treatment selection as in the General Introduction is given, but with additional selectivity and strength tests that are performed in case of a bad prognosis for walking performance. These tests can consist of grading of the performance of a squat. This information is important, because sufficient selectivity and strength are necessary for a successful outcome of SDR treatment. The (functional) hyper-resistance test and interactive gait lab could provide useful quantitative alternatives for these tests. In addition, they could expand their clinical value by measuring additional impairments.

The motorized hyper-resistance test focused so far on the identification of a few impairments. However, it has the potential to identify more, and link these to functional performance by measuring torque or position tasks. While these tasks do not directly represent walking, they can provide insight into reduced muscle force and the level of muscle co-contraction, and link this to the motor performance, in terms of deviation from the task or task fluency. To estimate the level of muscle selectivity, the muscle activation of the upper leg could be included in the analysis. To increase the representativeness of these measures, tasks could be adjusted to match normal gait.

While the validation of the interactive gait lab mainly focused on common gait analysis parameters, it has different potential features to identify impairments during gait. Next to measurement of hyperreflexia, the interactive gait lab has the potential

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Fig. 13-4. After the patient’s needs are assessed, the examination starts with the identification of possible underlying impairments, followed by gait analysis to determine the effect of these impairments on gait and their relation to the patient’s needs. If the negative effect of hyperreflexia on gait leads to a bad long term prognosis of walking performance, the selectivity and strength are tested, for instance by grading the performance of a squat. This is important, because sufficient selectivity and strength are needed for a positive outcome of a SDR, otherwise cutting of the roots will actually decrease a patient’s walking performance. Based on the outcomes of these tests, different treatments can be selected for a patient. Please note that this is a simplified representation of the complex clinical decision making, which normally also including other information, the existence of orthopedic problems and the opinion of patient and the parents.
Clinical implications

While directions for further research and development of the tests have been elaborately discussed in the previous part of the discussion, the presented work also holds several more direct clinical implications:

The motorized hyper-resistance test…
• provides an objective and standardized alternative for conventional clinical spasticity assessment and discriminates between neural and tissue impairments in calf muscles in children with spastic CP (older than 5 years; GMFCS I to III);
• should not be used interchangeably with manual (instrumented) tests that impose different rotations, since muscle response was found to be dependent on the movement profile;

The interactive gait lab…
• can be used as an alternative to the conventional overground lab to perform clinical gait analysis in ambulant children with cerebral palsy (older than 8 years, GMFCS I and II), provided that typical treadmill effects are taken into account during clinical interpretation of the outcome;
• facilitates force data measurement of sufficient quality over multiple consecutive strides during clinical gait analysis;
• provides a more real-life situation compared with conventional treadmill walking, as (1) its self-paced mode enables changes in walking speed due to natural variability or fatigue, and (2) its virtual reality allows for visual diversions and cognitive engagement;

The functional hyper-resistance test…
• has the potential to quantify stretch hyperreflexia directly during gait in ambulant patients with spasticity by applying belt accelerations and decelerations;

advantage to provide interactive feedback through the VR environment. Together with control of the walking speed, these tools can be used to challenge patients into changing their gait pattern and let them walk faster, more up-right, on their heels and toes, and with larger steps, fast forward swinging of their leg, and with raised knees, while diverting their attention from walking. These measurements can be used to disentangle gait limitations caused by impairments, and compensatory strategies that are used to deal with these limitations. Muscle activity recorded during different challenging tasks can be used to quantify the number of muscle synergies, estimate functional muscle strength, as well as quantify muscle co-contraction and abnor-
mal activation. The interactive environment can also provide direct feedback to the clinician, for instance on the effect of orthosis on the gait pattern of a patient, thus facilitating interactive tuning of ankle-foot orthoses during controlled walking and running. In addition, the SP walking mode could be used to study fatigue and gait variability. Finally, the split-belt control could be used to examine the ability to adopt the walking pattern to a changing environment, by running each belt at a different speed.

The interactive gait lab has been shown to facilitate the application of perturbations. The feasibility of estimating reflex activation and modulation has already been discussed. However, the response to perturbations can also be used to study the modulation of mechanical ankle properties, such as stiffness, quantify dynamic gait stability and examine causes of falling when this is part of the patient’s needs. Overall, the quantity of (potentially) available data does warrant for advanced statistical analysis to find the important pieces of the puzzle to characterize a patient, and select the optimal treatment by predicting its outcome.

**Thesis conclusion**

Advanced techniques to improve subject-specific precision diagnostics are becoming increasingly available. The work in this thesis has shown that the motorized hyper-resistance test can be used to differentiate between neural and mechanical impairments in patients with CP. In addition, a solid groundwork is established that proves that treadmill-based gait analysis can be used as an alternative to conventional gait analysis, and that SP and VR can be used interchangeably with their alternatives. Lastly, the first step has been taken to demonstrate the feasibility of hyper-resistance tests during treadmill-based gait analysis. These feasibility and validity studies prepared future introduction of these technologies into the clinic where comprehensive patient studies are needed to evaluate their ultimate clinical importance.

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