This dissertation generated new knowledge in the field of cardiovascular rehabilitation early after stroke. In this part of my thesis I would like to present and explain the innovative aspect of the approach, discuss the findings in a social and economic context, reveal the potential for further target groups, and propose approaches for translation into advanced robotic devices and rehabilitation strategies.

**Innovation**

Cardiovascular exercise has been shown to be effective in improving exercise capacity in chronic stroke [1]. In this thesis, I was able to provide first evidence that this is also true for subacute stroke survivors [2]. Intensive cardiovascular exercise interventions can be implemented safely in the early stages after stroke. Furthermore, first-ever evidence that cardiovascular fitness can be assessed in severely motor impaired stroke survivors using robotics-assisted technology was presented [3, 4] and a method for cardiovascular training in combination with task-specific exercise (i.e. walking) that is of high importance during early post-stroke rehabilitation was proposed [5]. To my knowledge, no other robotics-assisted device has been modified and equipped for cardiovascular rehabilitation early after stroke; therefore, the findings presented here are an innovation.

**Social and economic relevance**

Considering the social and economic burden of stroke, effective rehabilitation strategies have high potential to improve recovery and combat the rising costs that have been proposed in several health-care economic statements [6, 7, 8, 9]. The early initiation of exercise training aims to prevent deconditioning and to improve exercise capacity in regard to promote functional independence in daily life. To date, the improvement of cardiovascular fitness after stroke has not been set as a major rehabilitation goal, despite regular cardiovascular exercise having been shown to be able to improve exercise capacity and positively affect a variety of health-related factors [10, 11]. While mildly to moderately impaired individuals after stroke can participate in conventional exercise training programmes, the introduction of cardiovascular exercise in severely impaired stroke survivors presents unique challenges due to various motor limitations. Advanced rehabilitation technology might promote intensive cardiovascular fitness training for severely impaired populations. The improvements in exercise capacity will increase the chance of achieving independence in daily life, which, on a secondary basis, enables social participation and enhances quality of life. The implementation of cardiovascular exercise interventions as early as possible is expected to in-
crease the functional capacity level of stroke survivors, which might, in turn, decrease the overall expenses during inpatient care and after clinical discharge due to less need of health-care support. In addition, better cardiovascular fitness will decrease the risk for secondary medical complications and enable continuous participation in rehabilitation routines. Fewer adverse events during rehabilitation will lead to better therapy outcomes, and higher functional capacity levels are associated with higher independence during inpatient rehabilitation and after clinical discharge, which will further decrease health-care expenses. This thesis can be taken as a point of departure to further assess these assumptions about improved functional capacity level of stroke survivors on the one hand together with expected lower treatment costs on the other.

**Target groups**

The results reported in this dissertation are of importance for several populations suffering from severe motor impairments, which restricts the implementation of effective physical exercise interventions. Although we focussed on stroke due to its large socio-economic impact, the prevention of deconditioning and the improvement of functional capacity might be of interest in a variety of pathologies (e.g. heart failure, brain injury, spinal cord injury, multiple sclerosis, M. Parkinson). Sophisticated robotics-assisted concepts will enable the implementation of cardiopulmonary exercise testing and interpretation after severe medical events (e.g. soon after surgery).

To date, promising results in regard to improved cognitive function and enhanced neuroplasticity after cardiovascular exercise have been published [12, 13, 14, 15, 16]. The technology opens new perspectives in exploring specific effects of early initiation of cardiovascular stress in diseases presenting severe limitation for physical exercise.

The importance of early initiation of cardiovascular exercise and the feasibility using robotics-assisted technologies might also be of importance for the further design and development of advanced robotic concepts. Industries might implement the findings into novel product lines or for supplementary modules. Importantly, engineers and clinicians need to liaise closely.

**Translation of knowledge**

While robotic devices have been primarily developed to facilitate motor recovery, a hidden aspect is the potential for cardiovascular rehabilitation in severely disabled populations. The implementation of effective protocols to improve exercise capacity would provide a complement to the application of these devices for neurological rehabilitation, thus expanding the field of application and
clinical uptake. Our results have revealed the importance of early cardiovascular exercise admission after stroke [2] and demonstrated that feedback-controlled robotics-assisted treadmill exercise (FC-RATE) is a clinically feasible, reliable and repeatable concept for the assessment of exercise capacity in the early stages after severe stroke [4]. Furthermore, FC-RATE has been shown to be able to increase the exercise intensity to almost recommended levels for cardiovascular exercise training [5]. These findings have important implications for further development of assistive technologies and clinical rehabilitation strategies after stroke.

Based on the impact and importance of regular cardiovascular exercise after stroke, we propose further elaborations in control strategies for assisted physical exercise. A major goal will be the introduction of appropriate assist-as-needed strategies or on suitable error augmentation to facilitate cardiovascular stress while considering principles for motor learning. Although we have shown that severely motor impaired individuals can be assessed for cardiovascular fitness in a purely position-controlled path, advanced controllers might be essential to improve the reliability and the validity of cardiopulmonary assessments and increase the exercise intensity up to recommended levels for cardiovascular rehabilitation [17, 18].

Our results have led to further promising research activities in robotics-assisted technology. To date, several devices are on the market, which have the potential to provoke cardiovascular stress in severely impaired populations. Our research group is still working on the identification and evaluation of potential novel technology. For example, we recently explored a robotic-assisted stair climbing device [19]. Furthermore, a recent project has been initiated to develop highly specialised cardiopulmonary exercise testing modules for cardiovascular rehabilitation, which will be introduced to the market in the near future.

Although scientific statements reveal the impact of regular cardiovascular exercise training after stroke [16, 17] and there is evidence that conventional rehabilitation does not provide appropriate cardiovascular stress to induce training effects [20], the implementation of controlled intervention strategies to improve cardiovascular fitness has not taken place in many rehabilitation institutions. Our findings will, therefore, further emphasise the importance of intensive cardiovascular exercise during stroke rehabilitation. We propose a well-designed and structured cardiovascular rehabilitation strategy that is suitable for inpatient and outpatient settings. Trained medical staff need to categorise stroke survivors based on their cardiovascular and motor status at clinical entry, which enables the further allocation to adequate cardiovascular exercise programmes. Different intervention approaches within groups or on a single basis might then implement regular physical fitness training. While mildly to moderately impaired stroke survivors should perform on conventional devices (e.g. cycle ergometer, treadmill), or preferably participate in outdoor programmes
Valorisation

(e.g. Nordic walking), rehabilitation centres need to provide total-body recumbent steppers, body weight supported treadmills, robotics-assisted treadmills, or end-effector based gait trainers for the more severely impaired population. Indeed, these conventional methods can be boring due to their monotonous nature. However, further developments will introduce virtual reality setups to enhance motivation, and advanced strategies might shorten the time cost per session through the introduction of interval training methods. Due to the fact that FC-RATE was not able to reach recommended training intensities for cardiovascular rehabilitation, we propose high intensity interval training for further consideration. Controlled bursts of high work rate have shown promising results to improve exercise capacity in subacute stroke [21], and robotics-assisted treadmill technology might be able to achieve such short periods of peak performance.

**Conclusion**

It must be recognised that the improvement of cardiovascular fitness is an important rehabilitation goal after stroke. Based on the work presented in this thesis, it seems justified to strongly propose the implementation of intensive cardiovascular exercise programmes into early stroke rehabilitation. FC-RATE is a novel concept for assessment of cardiovascular fitness and improvement of exercise capacity in severely impaired individuals after stroke. The findings might be highly important in the prevention of deconditioning and the improvement of exercise capacity in a variety of diseases. Further developments in advanced robotic devices and control strategies will lead to better options in guiding cardiovascular exercise intensity, which will improve the application of cardiovascular rehabilitation strategies in severely impaired populations.

The age of technology in rehabilitation sciences has just begun. Rehabilitation robotics are still cost expensive, and elaborate setup structures and complex technical equipment complicate the implementation into clinical practice. It is hoped and expected, however, that the technology will profit from promising research findings that could facilitate an emerging demand, resulting in decreased acquisition costs for end-users.
References


186


Acknowledgment
The success of any project depends largely on the encouragement and guidance from a group of people. I take this opportunity to express my appreciation and thanks to all those who have been involved in this research project.

Prof. dr. Kenneth J. Hunt, my local supervisor, is an outstanding engineer and a wise character. You have been a tremendous mentor to me. I would like to thank you for giving me the opportunity to work on such an interesting project, encouraging me during the entire process, giving professional and personal advice, and for allowing me to grow as a scientist but also as a human being. Your advice on both research as well as on my personality have been priceless.

Prof. dr. Rob A. de Bie, my main supervisor, is a leader in rehabilitation research with a remarkable personality. I would like to thank you for guiding me through the PhD process as an external candidate at CAPHRI, giving me the opportunity to become an independent researcher, and encouraging me to think further. It was a pleasure being a PhD candidate in your research programme.

PD dr. Eling D. de Bruin, my independent supervisor, is an experienced and straightforward researcher with an outstanding methodological know-how. I would like to thank you for your scientific and personal advice throughout the entire process, and especially for your open ear and friendliness during difficult phases.

The Institute for Rehabilitation and Performance Technology at Bern University of Applied Sciences, my employer, is a centre of excellence for biomedical engineering in the field of rehabilitation technology. I would like to thank Matthias Schindelholz for his professional technical support, his reliability, and his honest personality. I also want to thank the entire academic staff for their valuable support, especially Lukas Bichsel, Marco Laubacher, Christian Dietrich, Jittima Saengsuwan, and Michael Muster. Special thanks go to Dr. Franz Baumberger: I appreciate your confidence and constant support.

The Reha Rheinfelden, our clinical cooperation partner, is a first-class rehabilitation centre in Northwestern Switzerland. I would like to thank Prof. Dr. Thierry Ettlin and Dr. Corina Schuster-Amt for the opportunity to perform experimental clinical research in their excellent facilities. I appreciate your faith in me. I especially would like to thank Heike Rosemeyer for her continuous support during clinical experimentation. Thank you for your critical inputs, your attention and support during the recruitment, and for your accurate work. I would also like to thank the clinical staff involved for their professional support, especially Dr. Niklaus Urscheler, Nadine Springinsfeld, Rahel Peyer, Daniel Vosseler, Michael McCaskey, Andrea Henneke, Heike Rösner, Doris Felber, Willi Bäckert, and Zorica Suica.
Acknowledgment

The "Herzpraxis am Rhein" is a cardiac private practice in Rheinfelden. I would like to thank Dr. Beat Spoendlin for his professional advice on the cardiac aspects of this project, and for the cardiopulmonary resuscitation courses. Also, many thanks to Dr. Andreas Rohner and Dr. Marco Kummer for the cardiac screening of the patients.

To all the participants that were involved in clinical research and whose interest stimulated them to participate in an unknown area of research: many thanks for your motivation, your efforts, and your confidence in our knowledge and in the technology.

I would also like to thank the members of the assessment committee and the corona for their time, interest, and valuable feedback: Prof. dr. Martin H. Prins, Prof. dr. Roger Gassert, Dr. Kenneth Meijer, Prof. dr. Robert Riener, and Prof. dr. Lodewijk W. van Rhijn.

I am very grateful for the scientific, personal, and even spiritual input and support of many people. A special thank goes to my paranymphs and classmates Corinne Ammann-Reiffer and Slavko Rogan. I would also like to thank Dr. Carolien Bastiaenen, Dr. Judith Sieben, and all my PhD classmates for their commitment.

Life consists of science and love. Words cannot express how grateful I am to have such wonderful people behind me. Many thanks to all my family members for their continual support, and to all of my friends who encouraged me to strive towards my goal and helped me to clear my mind.

Finally, I would like to thank my wonderful wife Sabina. This work would not have been possible without you. Thank you for your patience and for your unconditional love.