Preface

Rapid advances in microbubble pharmacology together with novel ultrasound technologies for contrast-specific imaging of the macro- and microcirculation have led to a number of exciting new applications for assessment of stroke patients. Now the possibility of performing ultrasound perfusion imaging has added new perspectives to the assessment of both ischemic and hemorrhagic stroke. First reports of real-time imaging of middle cerebral artery infarctions are emerging and new quantitative algorithms for assessment of regional cerebral blood flow are being applied for the first time in humans. Exciting new applications have been reported for visualization of plaque neovascularization and important advances are being made in the field of molecular imaging using targeted microbubbles. There is likewise growing interest in therapeutic applications of ultrasound, particularly in the field of sonothrombolysis. It is thus very timely to issue a supplement of *Cerebrovascular Diseases* which is devoted to current and emerging applications of cerebrovascular ultrasound and microbubbles.

Eleanor Stride from the Department of Mechanical Engineering at University College in London is an expert on the composition, synthesis and physical behavior of microbubbles. In her contribution to this supplement, she will explain what microbubbles are and why they are effective as imaging contrast agents. In addition, she will review how the physical behavior of microbubbles gives rise to a range of physical phenomena, which underlie their usefulness in therapeutic applications. This includes the important topic of microstreaming around oscillating microbubbles, which is thought to enhance cell permeability and, at higher intensities to produce an eroding

effect. Dr. Stride will also provide an introduction to our understanding of the interaction between microbubbles and cells at the molecular level to facilitate optimization of the use of microbubbles in therapeutic procedures.

Advances in microbubble pharmacology, of course, are essential for the exciting developments that are taking place in the field of cerebrovascular imaging and therapy. Technological ultrasound advances, however, are equally important in enabling these novel applications. We are honored that the engineers who have pioneered new technologies for contrast-specific imaging, namely Jeff Powers, Michalakis Averkiou and Matthew Bruce have agreed to contribute to this supplementary issue of *Cerebrovascular Diseases*. In their article, they will outline the advances in ultrasound imaging systems that have taken place over the past decade to enhance the visualization of contrast microbubbles. Through a review of basic ultrasound physics, they will help us understand how these new imaging developments work. They then describe novel imaging techniques as well as other features that are unique to ultrasound imaging of contrast agents.

Günter Seidel, a pioneer in the field of ultrasound perfusion imaging, and I have prepared a review of state-of-the-art contrast-specific imaging techniques for ultrasound evaluation of acute ischemic stroke patients. We elucidate the role of contrast-enhanced imaging for investigating the cerebral macro- and microcirculation and illustrate how contrast agents are used to diagnose various intracranial vessel abnormalities. We compare and critically evaluate different approaches for ultrasound perfusion imaging. Particular attention is given to the recent development of low mechanical index imaging,

which allows real-time visualization of stroke. We also address the application of microbubble replenishment kinetics as a possible avenue for obtaining quantitative information on local cerebral blood flow.

The identification of the vulnerable carotid artery plaque as a means for developing strategies to prevent stroke remains a hot topic of research. Histological studies have recognized that plaque inflammation and the presence of adventitial vasa vasorum, intimal angiogenesis and plaque neovascularization are strong predictors of instability in atheromatous lesions of cerebrovascular patients. The 'in vivo' study of these features has been the focus of several new imaging applications. Carotid ultrasound enhanced with ultrasound contrast agents is not only able to provide an improved assessment of the arterial lumen and plaque morphology, but can be used to directly visualize adventitial vasa vasorum and plaque neovascularization. This technique and its future clinical implications are discussed by the research team of Gian Luigi Lenzi from the University of Rome, which has already gained vast experience with this novel approach.

It is now known that transcranial B-mode ultrasound can detect intracranial hemorrhage (ICH) and hemorrhagic transformation (HT) with a high sensitivity and specificity. Nonetheless, the current diagnostic accuracy of transcranial ultrasound is not yet sufficient to support first-line therapeutic decisions. Thus, the most important application of transcranial ultrasound for assessment of ICH and HT remains bedside monitoring. According to recent studies, ultrasound perfusion imaging with microbubbles provides valuable additional information for the diagnosis of ICH and may differentiate ischemic from hemorrhagic stroke. Due to the typical reduction in contrast enhancement, parametric images provide good estimates and improved volume measurements compared with B-mode ultrasound alone in ICH patients. Karsten Meyer-Wiethe, Fabrizio Sallustio, and Rolf Kern will share their extensive experience on ultrasound imaging of intracerebral hemorrhages and HTs in their article entitled 'Diagnosis of Intracerebral Hemorrhage with Transcranial Ultrasound'.

Molecular or cellular imaging with contrast ultrasound relies on the selective targeting and retention of acoustically active contrast agents at sites of disease. Mi-

crobubble contrast agents remain entirely within the vascular space after intravascular administration and behave similarly to red blood cells within the microcirculation. Hence, microbubbles designed for molecular imaging are targeted to events that occur within the vascular compartment. Although this constraint limits the potential targets for microbubbles, there remain many targets of interest for evaluating pathophysiologic processes involved in cerebrovascular disease including angiogenesis, inflammation, and thrombus formation. The internationally esteemed research group led by Jonathan Lindner at the University of Oregon reviews their pioneer contributions to this rapidly advancing topic and presents new applications for cerebrovascular molecular imaging with ultrasound.

There is much interest in whether the treatment of acute ischemic stroke can be improved by ultrasound and microbubbles in combination with thrombolytic drugs. Despite many promising preclinical and first clinical results, the optimal techniques, indications, and contraindications have not yet been well defined. Details such as microbubble dosage, delivery, required thrombolytic drug dosage, and optimal ultrasound characteristics remain uncertain. The pioneer work of William Culp at the University of Arkansas has demonstrated that ultrasound and microbubbles may be effective in clot lysis of ischemic stroke without additional thrombolytic drugs. Moreover, both his work and our recent experimental studies in Mannheim suggest that targeting of thrombus with specific immunobubbles may improve the efficacy of sonothrombolysis without t-PA. Safety remains a major concern in the further development of ultrasound-enhanced thrombolysis and extensive animal work is required to define the most promising methods to translate into human application.

Thus, this supplement on ultrasound and microbubbles attempts to portray both current and future roles of ultrasound contrast agents in diagnosis and therapy of stroke. We hope that the articles, which have been written by esteemed international experts in their field, will provide both clinicians and researchers with a solid background for assessing the merits and possible shortcomings of these new developments.

Stephen Meairs