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Advanced Real-Time Imaging of the Medulla Oblongata: A Novel Biomarker in Essential Arterial Hypertension

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Abstract

High-resolution constructive interference in the steady state sequences were established as state-of-the-art imaging for the segmentation and three-dimensional visualization of complex neurovascular conflicts at the cranial nerve root entry zones. Detailed *in-vivo* imaging techniques analyzing the pathologic association between morphological neurovascular changes at the surface of the medulla oblongata and essential hypertension are still missing. We here in deal with a new translational technology of real-time magnetic resonance imaging for the *in-vivo* visualization of neurovascular compression in the posterior fossa. The opportunities of our real-time, dynamic imaging tools are presented with an example to provide an exquisite translation to the clinical and scientific implementation especially in younger patients with the focus on essential arterial hypertension.

Keywords: Real-time MRI; Essential arterial hypertension; Neurovascular compression; Medulla oblongata

Introduction

Neurovascular Compression (NVC) is described as an impressive pathological conflict between cranial nerves and vasculature at the surface of the brainstem [1-9]. There is evidence that essential arterial hypertension may be closely related to NVC. With the application of high resolution Magnetic Resonance Imaging (MRI) the individual neurovascular anatomy can be delineated in a Three-Dimensional (3D) fashion [6]. The authors described, that in 80 percent of the surgically treated patients a reduction and even normalization of blood pressure values could be achieved with Microvascular Decompression (MVD) [10]. The hypothesis is based on the model that aberrant pulsations of NVC at the RVLM excite at the afferent tracts of the nucleus tractus solitarii and the adrenergic C1-neurons, which respond in efferent signals to the sympathetic trunk in the thoracic spinal cord resulting in an activation of the intermediolateral nucleus [1-4]. This may lead to a higher vascular tone and positive inotropy of the heart resulting in arterial hypertension (Figure 1). The primary goal of this contribution is to evaluate the technical innovations of *in-vivo* ultra-fast real-time MRI in the visualization of individual pulsational characteristics of neurovascular compression at the medulla oblongata with the focus on frequent systemic diseases as essential arterial hypertension.

Materials and Methods

Real-time MRI data acquisition uses strongly radial gradient-echo sequences that use a turn-based sampling scheme that ensures spatial encoding by complementary sets of radial spokes in successive frames [8]. Typically, the pattern repeats every five frames, although other schemes are possible. Serial image reconstruction is achieved by calibration-less parallel imaging using nonlinear inversion. Nonlinear inversion extends iterative sense by formulating the image reconstruction as the solution to a nonlinear inverse problem [8]. The strategy optimally exploits all available data to simultaneously estimate all complex-valued coil sensitivity maps and the complex-value image. To achieve true real-time imaging, the reconstruction time per frame must be lower than the acquisition time. Therefore, a highly parallelized version of the algorithm was developed and implemented on a computer with multiple graphical processing units. In brief, image reconstruction is based on a convolution of the image with the point-spread function that can be implemented using a fast Fourier transform algorithm [8]. This requires only a single initial interpolation of the data onto two-fold oversampled grid, which is performed on the computer processing unit as a preprocessing step. The iterative reconstruction itself then uses only the fast Fourier transform algorithm, point-wise operations, and scalar products that can be performed very efficiently on Graphic Processing Units (GPUs). In this article real-time imaging was applied for the first time in the visualization

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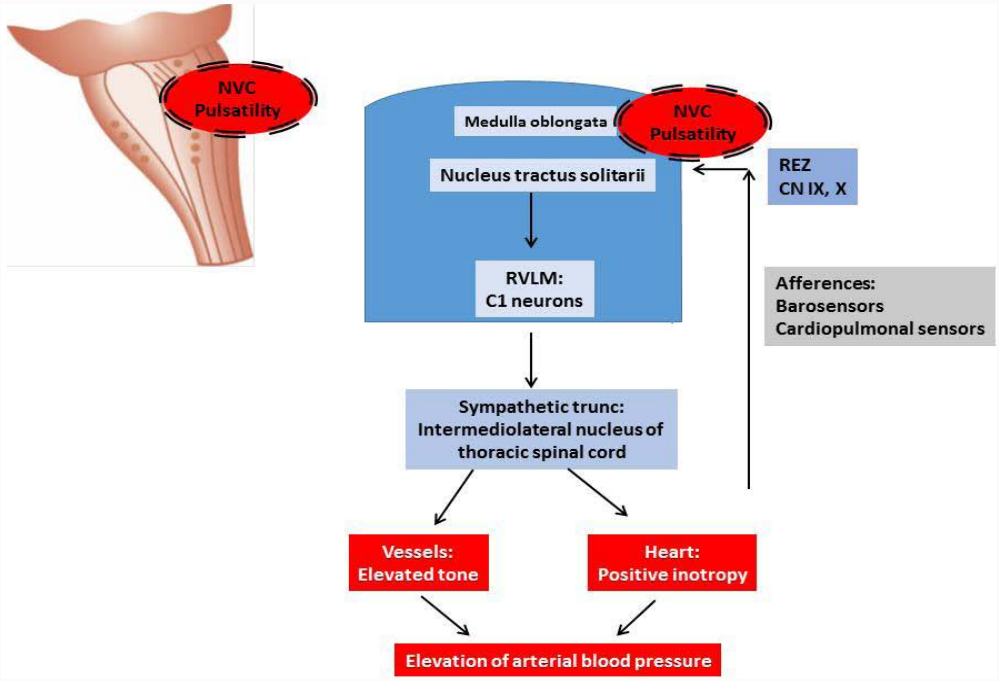

Figure 1: Here is a pathophysiological circuit model of neurovascular compression and essential hypertension presented. Note the pulsational changes of the neurovascular compression at the ventrolateral medulla oblongata containing the adrenergic C1-neurons and the root entry zones of the glossopharyngeal (IX) and vagus (X) nerves, which are connected to the peripheral vascular tone and heart action.

of the pulsation of neurovascular conflicts at the surface of the brainstem. The aim is to quantify the type of pulsatile compression and number of transferred pulse waves from the causative arterial vessel to the medulla oblongata in order to examine the translation of NVC to arterial hypertension of recruited hypertensive and normotensive subjects. For real-time of the posterior fossa highly T2-weighted images were continuously acquired with the following parameters: RF-spoiled radial FLASH, repetition time TR=5.6 ms, echo time TE=2.8 ms, flip angle 8°, field of view 128 × 128 and a slice thickness of 2 mm. Online reconstruction of real-time images was achieved by a highly parallelized version on a computer (sysGen/ TYAN Octuple-GPU, 2x123 Intel Westmere E5620 processor, 48GB RAM, Sysgen) with a 8 graphical processing units (GPUs, GeForce GTX TITAN, Nvidia).

Results and Discussion

We firstly performed a real-time MRI of the posterior fossa with the focus on neurovascular morphology and pulsational characteristics of the vertebral arteries in a healthy proband. A 3 Tesla MRI scanner (Prisma, Siemens Healthineers, Erlangen, Germany) with an equipped multi-GPU system for real-time MRI was applied. We were able to visualize the *in-vivo* pulsation of the vertebral arteries towards the ventrolateral medulla oblongata during diastole and systole. The pulsational pattern during heartbeat could be delineated with a narrow intravascular diameter during the diastolic phase and an enlarged intravascular diameter during the systolic phase. In the scanned moderately hypertensive proband one can see a distinct cerebrospinal fluid layer between the adventitia of the vertebral artery and the pial surface of the lower brainstem (Figure 2). There were no compromising vascular artifacts. Robust images were generated without the need for the application of contrast agents. The application of real-time *in-vivo* MRI of the vasculature at the surface of the brainstem was firstly presented in this article. An etiologic association between pulsatile neurovascular compression at the RVLM and essential arterial hypertension was described for a long time, but a detailed *in-vivo* investigation was not enabled in the human patient. With the advent of real-time MRI we aim to explore the very interesting and fascinating pulsational patterns of neurovascular conflicts and to explore any kind of relationship to the underlying pathologic blood pressure levels. In the clinical and scientific practice we were able to gain a highly robust and efficient approach for high-resolution imaging in order to examine a prospective series of hypertensive patients and normotensive probands in a multidisciplinary clinical trial. The further vision of our real-time imaging tool is the three-dimensional visualization of the acquired real-time MRI data with the generation of highly resoluted stack of stars sequences with the synchronization of the dynamic pulsation of NVC in correlation to the current blood pressure levels of the examined patients. We hope to achieve even higher spatial resolution by taking motion into account, and also desire to obtain dynamic information useful for the assessment of NVC. The aim is to categorize types of pulsatile compression and analysis of numbers of transferred pulse waves from the offending arterial vessels to the medulla oblongata. The pulsatility will be analyzed during the diastolic and systolic phases of the heartbeat. Especially the size of the affected area of the ventrolateral medulla by the pulsation of the offending vessel will be measured during diastole and systole. Individual vessel characteristics such as ecstatic vessel loops, rigidity of vessel walls and the impact of the pulsational affection at the lower brainstem will be analyzed. As limitations for our study we see, that invasive blood pressure analysis during the MRI acquisition will not be tolerated by each patient, so that we will trend to a non-invasive blood pressure measurement. Furthermore with this technique the question of lateralization of neurovascular compression for the appearance of essential arterial hypertension might be elucidated. An etiologic association of pulsatile neurovascular compression at

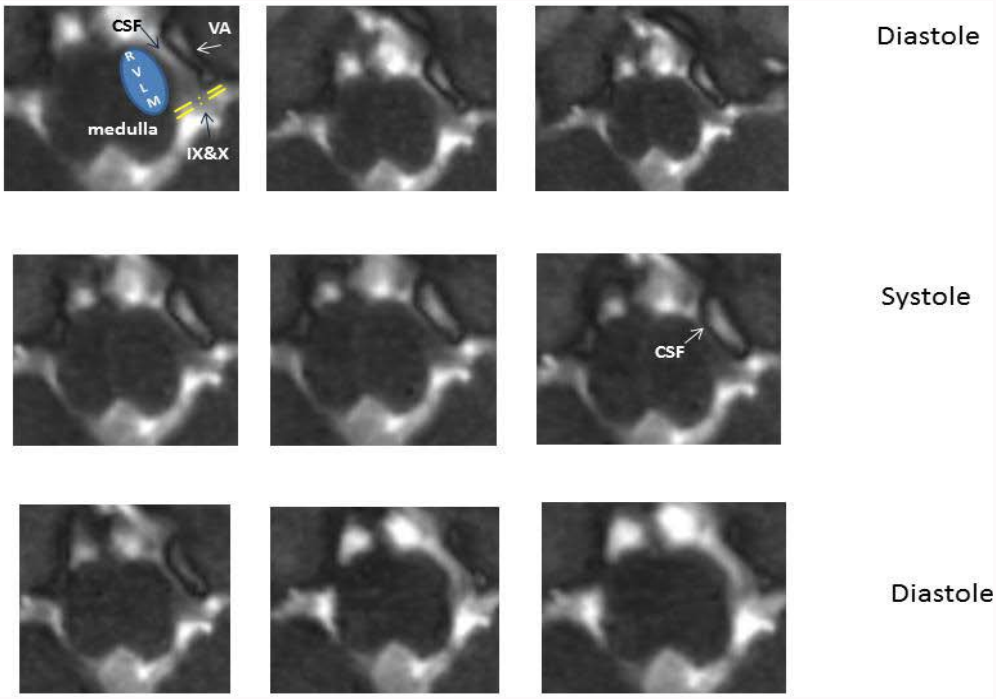

Figure 2: 33-year-old moderate hypertensive patient. Real-time magnetic resonance imaging to visualize the neurovascular relationships in the posterior fossa. This is a first-time visualization of real-time MRI of dynamic pulsation of the vertebral arteries towards the Rostral Ventrolateral Medulla Oblongata (RVLM) during diastole (first and last row) and systole (middle row) contacting the presumed course of the fascicles of the glossopharyngeal and vagus nerves. Note that during diastole the luminal diameter of the left-sided Vertebral Artery (VA) is physiologically narrow and widened during the systolic phase and potentially pushing towards the medulla oblongata in the moderately hypertensive proband, where a very distinct narrow Cerebrospinal Fluid (CSF) corridor can still be determined between the artery and the brainstem (CSF: Cerebrospinal Fluid; RVLM: Rostral Ventrolateral Medulla Oblongata; VA: Vertebral Artery; IX: Glossopharyngeal Nerve; X: Vagus Nerve).

the RVLM to arterial hypertension is widely discussed and there are missing clear translational criteria in accurate patient selection for neurosurgical treatment. We herein aim to receive more information on the pathophysiology of the underlying neurovascular compression for the maximum validation of a potential surgical therapy especially in younger hypertensive patients, who have therapy-refractory blood pressure levels with a multiple dosing of antihypertensive agents.

Conclusion

An etiologic association of pulsatile neurovascular compression at the RVLM to arterial hypertension is widely discussed and there are missing clear translational criteria in expedient patient selection for neurosurgical treatment. This article deals with the perspective application of real-time magnetic resonance imaging for the *in-vivo* visualization of pathological neurovascular relationships at the brainstem. We aim to develop novel imaging biomarkers based on state-of-the-art MRI methods. Advanced image analyses tools including machine learning will be used to identify imaging biomarkers that are correlated with essential arterial hypertension. Dynamic imaging approaches to visualize pulsating vessels and to extract new quantitative information which is not accessible in traditional imaging approaches in a consecutive series of hypertensive patients will be explored. This will be based on fast two or three-dimensional non-Cartesian sequences developed for originally or cardiac imaging and used together with advanced image reconstruction for real-time imaging.

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