Truly non-invasive NMR determination of peripheral vascular resistance by combining dynamic angiography and arterial spin labeling techniques

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Introduction. The determination of peripheral vascular resistances, at rest and in response to vasoconstrictor or vasomotor stimuli, is crucial for assessment of arteriolar dysfunction. It requires simultaneous determination of organ perfusion and systemic arterial pressure. Arterial spin labeling (ASL) combined to NMR imaging can be used to quantify tissue perfusion non-invasively with high temporal and spatial resolutions including in small animals. To our knowledge, arterial pressure of small animals can only be measured invasively during NMR studies, using an indwelling arterial catheter connected to pressure transducer. The objective of this study was first to develop a fully non-invasive NMR method to measure systolic and diastolic blood pressures in small animals and second to combine this method with ASL measurement of perfusion in order to evaluate local peripheral resistance exclusively from data sets acquired non-invasively.

Materials and methods. Experiments were performed with a Bruker *Biospec* 4T NMR system equipped with a 20cm diameter 200mT.m^{-1} gradient insert. They were carried out on adult Wistar rats (Charles River Labs, France). Animals were anaesthetized with 2% of isoflurane in medical air delivered at 1.5l.min^{-1} and were placed in supine position on a heating pad. The experimental set up consisted in three ^{1}H coils, one volume birdcage transmitter and two surface receivers, with active decoupling. Perfusion and angiography sequences were run alternatively and corresponding signals were acquired separately in the leg and in the tail, respectively.

NMR quantification of skeletal muscle perfusion: perfusion was measured in the *gastrocnemius* muscle using SATIR, a pulsed ASL variant developed in our lab [1] (ASL labeling time: 1.3s, TR: 8s, inter-echo spacing: 2.9ms, in-plane resolution: 0.39x0.93mm^2).

NMR determination of arterial pressure: it was based on the tail cuff method. The rat caudal artery was subjected to an external pressure from a monitoring air cuff applied to the tail base. Arterial occlusion was followed by progressive and controlled air cuff deflation (10mmHg step every 10s). Arterial inflow signal was collected during cuff release by single-slice dynamic NMR angiography, using a rapid gradient echo FLASH sequence [2] (TR: 20ms, TE: 2.6ms, α: 70°, slice thickness (ST): 3 mm, ST/TR[blood velocity saturation limits]=15cm.s^{-1}, in-plane resolution: 119x160um^2, image acquisition time: 2.56s). Signal intensity was measured from two ROIs in the caudal artery and one vein respectively.

Standard arterial pressure measurements: we used both indirect technique by tail air cuff (Letica *LE 5001*; flow information acquired by strain gauge sensor) and direct invasive technique from an exteriorized catheter implanted in the carotid (Gould *P50* Pressure transducer connected to Hellige strip chart recorder).

Protocol. Validation of NMR arterial pressure measurement: four female Wistar rats were instrumented with an indwelling catheter in the carotid artery. NMR angiography and invasive arterial pressure measurements were simultaneously performed. Arterial pressure was challenged by intraperitoneal injections of hypertensive (norepinephrine: 0.4-1mg) or hypotensive (pentobarbital: 0.5-1mg) agents. In addition, indirect arterial pressure measurements were performed on each animal just before and after the NMR acquisitions in baseline conditions.

Peripheral vascular resistance: muscle perfusion and arterial pressure NMR measurements were interleaved on four normal female Wistar rats at rest.

Results. *Fig.1* shows the typical temporal time-course of arterial and venous inflow intensities in rat tail during cuffing. Arterial inflow was characterized by five steps: **1** and **5**: free steady state conditions; **2**: vascular occlusion; **3**: progressive increase of arterial inflow signal while cuff pressure was comprised between systolic and diastolic pressure. Systolic and diastolic pressures are identified as inflexion points of step 3; **4**: transient flow decrease due to finite venous compliance. During this step, the shapes of the venous and arterial curves depend on venous capacity and compliance relative to cumulated arterial flow during cuff release. Correlations between NMR and standard arterial pressure measurements are shown in *fig.2* and validate our method. *Table1* displays four examples of peripheral vascular resistance values calculated in rat *gastrocnemius* muscle at rest from arterial pressures and perfusion measured by NMR.

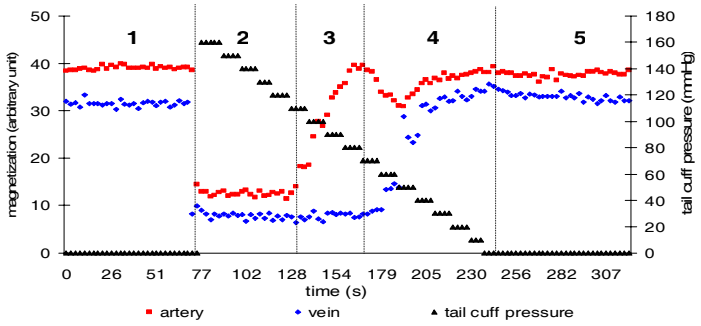

Fig.1: time-course of arterial and venous angiographic signals (left scale) and cuff pressure (right scale)

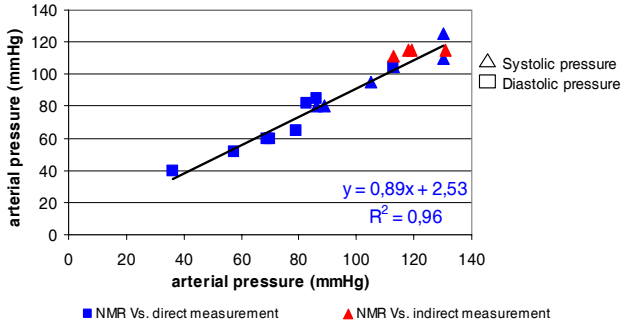

Fig.2: NMR VS direct/indirect arterial pressure measurements

Conclusion. In this work, we developed and validated a fully non-invasive NMR set up to quantify peripheral vascular resistance in the rat by combining measurements of perfusion by ASL-NMR and arterial pressure by dynamic angiography associated to tail cuffing. Truly non-invasive and integrated investigations of the arteriolar dynamics, including vasodilation reserve, will be possible in small animals using such functional NMR protocols.

References. 1-Raynaud J.S., et al., MRM 2001 **46(2)**: 305-11.
2-Vanhoutte G., et al., NMR Biomed. 2002 **15(4)**: 263-9.

	Rat 1	Rat 2	Rat 3	Rat 4
Systolic arterial pressure (mmHg)	105	80	115	80
Diastolic arterial pressure (mmHg)	72	60	80	70
Mean arterial pressure (mmHg)	88.5	70	92.5	75
Gastrocnemius muscle perfusion (ml.min^{-1}.100g^{-1})	16	8	10	9.5
Muscle vascular resistances (mmHg.ml^{-1}min.100g)	5.5	8.7	9.25	7.9

Table1: arterial pressure and *gastrocnemius* muscle perfusion determined by NMR and calculated vascular resistances at rest