In vivo detection of catecholamines by magnetic resonance spectroscopy: A potential specific biomarker for the diagnosis of pheochromocytoma

Alessio Imperiale, MD, PhD,[a,b] Stephanie Battini, PhD Stud,[b] Gerlinde Averous, MD,[c] Didier Mutter, MD, PhD,[d] Bernard Goichot, MD, PhD,[e] Philippe Bachellier, MD, PhD,[f] Karel Pacak, MD, PhD,[g] David Taïeb, MD, PhD,[h,i] *and* **Izzie-Jacques Namer, MD, PhD,[a,b]** *Strasbourg and Marseille, France, and Bethesda, MD*

From the Department of Biophysics and Nuclear Medicine,[a] University Hospitals of Strasbourg; ICube, UMR (Unité Mixte de Recherche) 7357 University of Strasbourg/CNRS (Centre National de la Recherche Scientifique) & FMTS (Fédération de Médecine Translationnelle de Strasbourg),[b] Faculty of Medicine of Strasbourg; Department of Pathology,[c] University Hospitals of Strasbourg; Department of General, Digestive and Endocrine Surgery,[d] IRCAD-IHU, University Hospitals of Strasbourg; Department of Internal Medicine, Diabetes and Metabolic Disorders,[e] University Hospitals of Strasbourg; Department of Visceral Surgery and Transplantation,[f] University Hospitals of Strasbourg, Strasbourg, France; Program in Reproductive and Adult Endocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development,[g] National Institutes of Health, Bethesda, MD; Department of Nuclear Medicine,[h] La Timone University Hospital, CERIMED, Aix-Marseille University, Marseille, France; and Inserm UMR1068 Marseille Cancerology Research Center,[i] Institut Paoli-Calmettes, Marseille, France

Pheochromocytoma (PHEO) is a catecholamine-secreting tumor that originates from the chromaffin cells of the adrenal medulla. The diagnosis of pheochromocytoma relies on an increase of plasma or urinary metanephrines. Concomitant disease as kidney failure, however, may be associated with false-positive results.[1] Moreover, nonsecreting PHEOs are not exceptional.[2,3]

Medical imaging plays a crucial role in the evaluation of PHEO. Magnetic resonance imaging (MRI) has high sensitivity but limited specificity.[4,5] Radionuclide imaging also may contribute to the characterization of adrenal masses with high specificity but uses ionizing radiation.[6]

Catecholamines can be detected by ex vivo analysis of intact tumor samples by the use of ^{1}H high-resolution magic-angle spinning nuclear magnetic resonance (^{1}H-HRMAS NMR) spectroscopy. The 3,4-dihydroxybenzene group characteristic of both adrenaline and noradrenaline generates an NMR signal that can be easily recognized and quantified.[7]

The objective of this study was to evaluate the clinical reliability of catecholamine in vivo detection by proton magnetic resonance spectroscopy (1H-MRS). In 2014, 2 patients were referred to the Medical Imaging Department of the University Hospitals of Strasbourg for evaluation of adrenal masses. The first patient, a 52-year-old man, had typical symptoms of PHEO with increased 24-hour urinary normetanephrine (6,439 nmol/24 hr, upper reference limit <2,293) and metanephrine (3,646 nmol/24 hr, upper reference limit <1,515) values. Results of an MRI scan revealed a right adrenal tumor measuring 50 mm in diameter with atypical features (Fig 1, *A*). The second patient, a 32-year-old man, presented with a nonsecreting adrenal incidentaloma. Results of an MRI scan revealed a 40-mm right adrenal tumor with typical features of adenoma (Fig 2, *A*). Respiratory-triggered single-voxel 1H-MRS was performed in addition to standard MRI acquisition before the injection of gadolinium on both tumors (Fig 1, *B*, and Fig 2, *B*). According to previous reports,[7,8] spectral analysis also was

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Reprint requests: Alessio Imperiale, MD, PhD, Service de Biophysique et de Médecine Nucléaire - Hôpital de Hautepierre, 1, Avenue Molière, 67098 Strasbourg Cedex, France. E-mail: alessio.imperiale@chru-strasbourg.fr.

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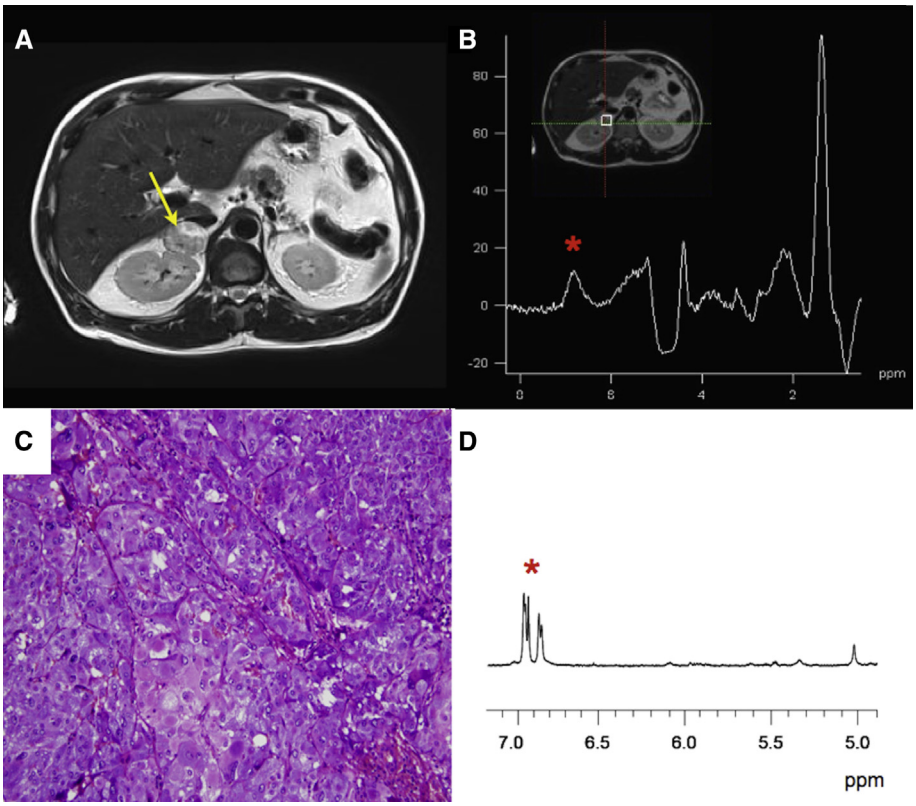

Fig 1. Results of upper abdomen MRI (*A*), in vivo respiratory-triggered proton single-voxel ^{1}H-MRS (*B*), and ex vivo ^{1}H-HRMAS NMR (*D*), respectively, performed in a pheochromocytoma (*C*). The signal detected at about 7 ppm (*) corresponds to the spectral signature of the catecholamine-specific 3,4-dihydroxybenzene group detected in pheochromocytoma by respiratory triggered single voxel ^{1}H-MRS then confirmed by ^{1}H-HRMAS NMR.

in the 4.7–9 ppm range for catecholamine assessment.

As expected, the tumor from the first patient exhibited a clear signal on respiratory triggered single voxel 1H-MRS study at approximately 7 ppm (Fig 1, *B*), corresponding to the spectral signature of the catecholamine-specific 3,4-dihydroxybenzene group, thus pointing towards the presence of PHEO. These findings were then confirmed by histopathology (Fig 1, *C*) as well as ex vivo ^{1}H-HRMAS NMR spectroscopy (Fig 1, *D*). In the second case, no tumor catecholamine content was detected on either in vivo (Fig 2, *B*) and ex vivo spectroscopy (Fig 2, *D*) and the histopathologic diagnosis confirmed the presence of adrenocortical adenoma (Fig 2, *C*).

This is the first report demonstrating a head-to-head comparison between in vivo and ex vivo NMR spectroscopy for the detection of catecholamine-secreting tumors. It also suggests that in vivo assessment of tumoral catecholamines might play a unique role in the differential diagnosis of adrenal tumors to confirm or rule out the presence of PHEO, especially in unusual situations.[1,9] It is also expected that this new approach will play an important role in the assessment of therapeutic responses of PHEO by monitoring catecholamine content in these tumors.

In conclusion, respiratory-triggered proton ^{1}H-MRS could be represent a functional, noninvasive, and nonionizing technique in the diagnosis of PHEO; however, the clinical utility of respiratory triggered single voxel ^{1}H-MRS needs to be further evaluated in a larger series of patients with adrenal incidentalomas that also includes more challenging situations such as cystic, hemorrhagic, and nonsecreting PHEOs, which are characterized from slightly high or completely absent of catecholamine secretion. Moreover, a comparison between respiratory-triggered single voxel ^{1}H-MRS and radionuclide imaging techniques (ie, ^{123}I-metaiodobenzylguanidine scintigraphy, ^{18}F-fluorodihydroxyphenylalanine positron emission tomography) would be of particular interest for a definitive validation.

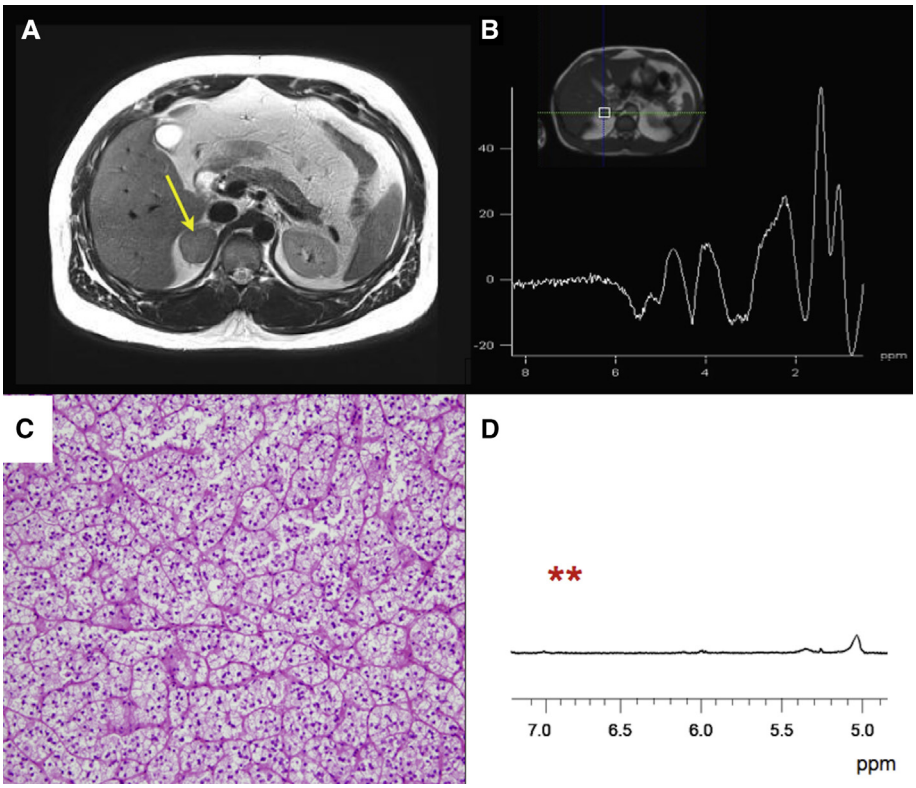

Fig 2. Results of upper abdomen MRI (*A*), in vivo respiratory-triggered single-voxel ^{1}H-MRS (*B*), and ex vivo ^{1}H-HRMAS NMR (*D*), respectively, performed in adrenocortical adenoma (*C*). No catecholamine-specific signal was detectable neither by ^{1}H-MRS nor by ^{1}H-HRMAS NMR (**) at about 7 ppm.

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