Hepatic parenchymal enhancement at Gd-EOB-DTPA-enhanced MR imaging: correlation with morphological grading of severity in cirrhosis chronic hepatitis

PASTOR, Catherine
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To the Editor:

I have read with great interest a recent article published in your journal by Kanki et al. [1] entitled “Hepatic parenchymal enhancement at gadolinium-ethoxybenzyl-diethylene-triamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging MR imaging: correlation with morphological grading of severity in cirrhosis and chronic hepatitis.” As observed by the authors, no correlation was found between the severity of chronic hepatitis or cirrhosis and the parenchymal enhancement in the hepatobiliary phase of magnetic resonance (MR) imaging with Gd-EOB-DTPA. Thus, the decreased number of hepatocytes and/or increased fibrosis would not lead to a decreased hepatic enhancement. Persistence of a high enhancement in surrounding cirrhotic tissues would not alter the detection of focal lesions, with the contrast between parenchyma and lesions being preserved.

For the authors, the persistence of high enhancement within cirrhotic tissues was puzzling, and I would like to add a cellular insight to better understand such observations. There are two ways for Gd-EOB-DTPA-enhanced MR imaging to induce low signal intensities in cirrhosis: a decreased expression (and/or function) of the membrane transporters organic anion transporting polypeptides (OATP1B1 and OATP1B3) (with a concomitant decreased uptake of the contrast agent) and/or an increased extracellular volume associated with an increased volume of septa. However, once Gd-EOB-DTPA had entered into hepatocytes, the cell concentrations (and signal enhancement) would depend on the bile excretion of the contrast agent through the canalicular transporter multiple resistance-associated protein (MRP) 2. Thus, if MRP2 is functional, Gd-EOB-DTPA would be excreted into bile, and the low concentrations that had entered into cells would not accumulate in cells. In contrast, when the expression or function of MRP2 is decreased, the low amount of Gd-EOB-DTPA taken up by cirrhotic hepatocytes would be trapped within cells, and hepatic enhancement would remain high.

Few publications investigated the expression of OATP1B1, OATP1B3 and MRP2 in cirrhosis. In liver parenchyma surrounding focal lesions, the expression of OATP1B1, OATP1B3 and MRP2 is decreased in chronic hepatitis C infection [2] (Fig. 1). The expression of transporters was further decreased in cirrhosis. Thus, a simultaneous decreased in both uptake and exit membrane proteins might explain a persistent high enhancement. When we injected Gd-BOPTA in rat livers lacking Mrp2, the hepatic accumulation of the contrast agent was similar to that observed in normal livers, despite a low uptake of Gd-BOPTA through rat uptake transporters, with Gd-BOPTA being trapped within hepatocytes in the absence of bile excretion [3,4]. Moreover, human hepatocellular carcinoma can be hyperintense in comparison to surrounding tissues when Gd-EOB-DTPA is trapped within pseudoglands or in tumoral cells lacking Mrp2 on the canalicular membrane [5].

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Thus, Gd-EOB-DTPA-enhanced MR imaging is an important opportunity to measure the accumulation of Gd-EOB-DTPA in injured hepatocytes. However, signal intensities obtained in the hepatobiliary phase reflect the cooperation between uptake and exit transport systems. This point may explain high enhancement in cirrhotic livers.

Catherine M. Pastor
Laboratoire de Physiopathologie Hépatique et Imagerie Moléculaire
Hôpitaux Universitaires de Genève
1205 Geneva, Switzerland
E-mail address: catherine.pastor@hcuge.ch

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References


Skeletal muscle mitochondrial function cannot be properly inferred from PCr resynthesis without taking pH changes into account

To the Editor:

We have read with much interest the paper recently published by Khushu et al. regarding the impaired muscle metabolism in hypothyroid patients [1]. Although the results of this investigation are of potential interest, we are actually concerned about the utilization of the phosphocreatine recovery rate constant (kPCr) as a simple index of mitochondrial function and the corresponding conclusions regarding the impact of hypothyroidism on muscle metabolism during exercise. The real issue is actually to clearly determine whether one can infer about mitochondrial function on the basis of PCr rate constants measurements.

During recovery from exercise, PCr is resynthesized purely as a consequence of oxidative adenosine triphosphate (ATP) synthesis [2], and measurements of the kPCr have been used in order to characterize mitochondrial function in a variety of conditions [3]. However, several studies have clearly demonstrated that cytosolic pH has a strong influence [3]. It is actually well acknowledged that kPCr is inversely related to the extent of intracellular acidosis and PCr consumed [3]. In other words, a significant intracellular acidosis and a large PCr consumption in exercising muscle would be associated with a slower PCr resynthesis [3]. In the Khushu et al. study, cytosolic pH was found to be significantly lower after a 6-min constant-load plantar flexion exercise in hypothyroid patients compared to controls (6.95 ±0.02 vs. 7.02±0.06, respectively). Therefore, the conclusions of an altered mitochondrial function in hypothyroid patients [1] on the single basis of kPCr measurements have to be interpreted cautiously. Of note, several kinetic parameters are commonly used to describe PCr changes during exercise-to-recovery transition, including kPCr, the initial rate of PCr recovery (ViPCr) and the maximum aerobic capacity (Qmax) [4]. These three parameters characterizing PCr resynthesis are correlated to oxidative capacity. However, in contrast to kPCr, ViPCr and Qmax are insensitive to exercise intensity and end-of-exercise metabolic conditions [3]. On that basis, ViPCr and Qmax should be considered as additional indices to compare the postexercise PCr recovery rate and mitochondrial oxidative capacity across different populations when end-of-exercise pH and PCr concentration values are different or not taken into account. These additional parameters were considered in some previously published studies which investigated in vivo mitochondrial function from childhood to young and/or late adulthood [5,6]. In contrast, these parameters were not taken into account in other studies which investigated age-related changes in mitochondrial oxidative capacity from childhood to adulthood [7] and examined the association between mitochondrial alterations and insulin sensitivity in overweight and normal-weight children [8]. In the Khushu et al. study, the Qmax calculation was oversimplified as the product of kPCr and the resting [PCr], as previously described [9]. This oversimplification is actually derived from the calculation of the ViPCr from an exponential fitting. In that case, ViPCr is represented by the product of kPCr and the amount of PCr consumed at the end of exercise. On that basis, a few authors have calculated Qmax similarly to ViPCr, with the amount of PCr consumed being replaced by the resting [PCr]. Although mathematically plausible, this calculation is not supported by any control model, and the corresponding Qmax is devoid of any enzymatic meaning, as it is the case for the calculation of Qmax using ADP within a Michaelis–Menten framework. This method is then largely questionable because it ignores the commonly accepted theory considering adenosine diphosphate as a key regulator of oxidative ATP synthesis [10]. In addition, with such an approximate calculation, Qmax becomes strongly dependent on kPCr and/or [PCr] measured at rest. In their study, Khushu et al. [1] reported no significant difference in the resting [PCr] values between hypothyroid patients and controls (43.6±0.8 mmol kg⁻¹ vs. 42.0 ±1.0 mmol kg⁻¹, respectively). Given that the resting [PCr] values were similar, the corresponding calculated Qmax...