Cardiac Remodeling in Hypertension: Clinical Impact on Brain, Heart, and Kidney Function

Authors
Sophie Mavrogeni[1], George Piaditis[2], Flora Bacopoulou[3], George P. Chrousos[4]

Affiliations
1 Cardiology, National and Kapodistrian University of Athens, Athens, Greece
2 Department of Endocrinology and Diabetes, Errikos Ntynan Hospital Center, Athens, Greece
3 Pediatrics, National and Kapodistrian University of Athens, Athens, Greece
4 First Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece

Key words
hypertension, magnetic resonance imaging, heart, brain, kidneys

received 01.01.2022
accepted after revision 03.03.2022
published online 29.03.2022

Bibliography
Horm Metab Res 2022; 54: 273–279
DOI 10.1055/a-1793-6134
ISSN 0018-5043

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Prof. Sophie Mavrogeni
Onassis Cardiac Surgery Center
Cardiology Dept.
50 Esperou Street, P.Faliro
17561 Athens
Greece
Tel.: + 302109882797, Fax: + 30-2109882797
soma13@otenet.gr

ABSTRACT

Hypertension is the most common causative factor of cardiac remodeling, which, in turn, has been associated with changes in brain and kidney function. Currently, the role of blood biomarkers as indices of cardiac remodeling remains unclear. In contrast, cardiac imaging, including echocardiography and cardiovascular magnetic resonance (CMR), has been a valuable noninvasive tool to assess cardiac remodeling. Cardiac remodeling during the course of systemic hypertension is not the sole effect of the latter. "Remodeling" of other vital organs, such as brain and kidney, also takes place. Therefore, it will be more accurate if we discuss about "hypertensive remodeling" involving the heart, the brain, and the kidneys, rather than isolated cardiac remodeling. This supports the idea of their simultaneous assessment to identify the early, silent lesions of total "hypertensive remodeling". In this context, magnetic resonance imaging is the ideal modality to provide useful information about these organs in a noninvasive fashion and without radiation. For this purpose, we propose a combined protocol to employ MRI in the simultaneous assessment of the heart, brain and kidneys. This protocol should include all necessary indices for the evaluation of "hypertensive remodeling" in these 3 organs, and could be performed within a reasonable time, not exceeding one hour, so that it remains patient-friendly. Furthermore, a combined protocol may offer "all in one examination" and save time. Finally, the amount of contrast agent used will be limited granted that post-contrast evaluations of the three organs will be performed after 1 injection.

Introduction

Cardiac remodeling (CR) is the end-point of any change in cardiac anatomy and/or function occurring as a response to physiologic or pathologic stimuli, such as exercise, cardiac lesioning, hemodynamic alterations, and inflammatory or neurohormonal processes. CR may lead to myocyte death/fibrosis and, ultimately, cardiac dysfunction [1]. CR is associated with increased left ventricular (LV) volume and reduced LV ejection fraction (LVEF), leading to heart failure (HF) with reduced ejection fraction (HFrEF). Its reversal, known as reverse remodeling, usually leads to clinical improvement [1].

During normal aging, a decrease in compliance may provoke increased pulse wave velocity, systolic blood pressure, and LV afterload. In response to these changes, the myocardium remodels to maintain its function. These adaptive mechanisms, although not

necessarily pathologic, may increase the susceptibility for myocardial ischemia and HF [2].

Diffuse cardiac fibrosis may also be the result of normal aging, contributing to progressive cardiac stiffening even in the absence of overt cardiovascular disease [2]. Stiffening can be associated with either contraction or relaxation [3]. However, in aging humans, the contractile function of the heart is preserved even if its relaxation ability is significantly reduced, due to stiffening [4]. This is the result of cardiac sympathetic nervous system stimulation that increases heart contractile function and allows maintenance of normal cardiac output in the aging population [5]. On top of this, the increased activity of the sympathetic nervous system is a risk factor for induction of ventricular fibrillation, especially after a myocardial infarction [6].

Hypertension represents the main cause of mortality worldwide [2] and is the most common cause of extensive cardiac remodeling, including abnormal activity of the cardiac sympathetic nervous system, hypertrophy, and interstitial fibrosis. These processes are well documented risk factors for ventricular fibrillation and HF [7]. LV hypertrophy, defined as an abnormal increase in LV mass, is an adaptive mechanism that increases cardiac workload achieved by reduction of wall stress and normalization of LVEF [7]. However, cardiac remodeling may be associated with increased incidence of adverse effects [8].

In parallel with cardiac muscle hypertrophy, diffuse heart fibrosis may also occur in hypertension. While the role of hypertrophy is acknowledged as a compensatory mechanism [7], diffuse fibrosis of the heart is a pathologic process potentially contributing to arrhythmias and diastolic/systolic dysfunction [9]. Fibrosis plays an important role in the pathophysiology of hypertensive heart disease (HHD), with the associated accumulation of collagen compromising relaxation, diastolic suction, and passive blood filling, leading to diastolic dysfunction. These alterations further compromise cardiomyocytes' contraction leading to impaired systolic function [9]. In addition, perivascular fibrosis contributes to impaired coronary flow reserve (CFR), through external compression of intramural coronary arteries, while interstitial fibrosis may lead to ventricular arrhythmias [5]. Finally, HHD patients with arrhythmias have higher deposit of myocardial collagen than those without arrhythmias, despite similar LVEF and CAD incidence [10]. Fibrosis may also induce conduction abnormalities by promoting local reentry arrhythmias [10].

Blood biomarkers for cardiac remodeling evaluation

It is clear that there is an association between serially measured circulating natriuretic peptides and LV remodeling. In the PROTECT (ProBNP Outpatient Tailored Chronic HF Therapy) study, 151 outpatients with HF and LVEF < 40 % were randomized to either standard-of-care management or standard care and the additional goal of reducing N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration to < 1000 ng/l over 10 months [11, 12]. Patients with greater reduction in NT-proBNP presented greater improvement in LVEF, indexed LVESV, and LV end-diastolic volume (LVEDV). After guideline-directed medical therapy, NT-proBNP concentrations < 1000 ng/l were also associated with significant amelioration of LV diastolic function and RV systolic function and reduction of mitral regurgitation. A pre-specified echocardiographic analysis from the recently completed GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial examined degrees of reverse remodeling associated with changes in NT-proBNP concentrations in 269 patients under medical treatment. This analysis showed a reduction in LV volumes and improvement in LVEF proportional to the NT-proBNP reduction [13]. Many HF treatments, including both drugs and cardiac resynchronization (CRT) were associated with NT-proBNP reduction and reverse remodeling [14].

Furthermore, high-sensitivity troponin allowed accurate quantification of cardiomyocyte death. In a study of HF patients due to various causes and LVEF < 40 %, those with high-sensitivity troponin T < 11 ng/l had the highest rate of reverse remodeling during follow-up [15]. Finally, In HHD, Cardiovascular Magnetic Resonance (CMR)-measured LV mass and cardiac geometry are independently associated with established biomarkers of myocardial stretch and injury: The greater the cardiac mass and dimension, the greater the concentration of NT-proBNP and hsTroponin T [16].

Soluble suppression of tumorigenesis-2 (sST2) is a promising biomarker of cardiac remodeling [17]. In the heart, sST2 is released by cardiomyocytes and fibroblasts under stress and blunts the antifibrotic effects of interleukin-33. In outpatients with HFrEF, sST2 concentrations are associated with LV remodeling. Finally, a low sST2 was an independent predictor of reverse remodeling [18, 19].

Galectin-3 (Gal-3), a soluble beta-galactosidase binding lectin, participates in the development of cardiac fibrosis and remodeling after myocardial infarction (MI), but also in known HF. Gal-3 may gradually increase with the aggravation of myocardial fibrosis, which is the main characteristic of HHD [20]. Furthermore, Gal-3 may be involved in the development and progression of hypertension complicated with diastolic dysfunction. Its concentration increases with cardiac dysfunction, but significantly decreases after treatment and therefore, Gal-3 concentration before treatment can be used as a predictor of treatment efficacy [21].

Other biomarkers that may be potentially used for the evaluation of cardiac remodeling include mimecan and other indicators of extracellular matrix turnover, such as bone morphogenetic protein (BMP-1), carboxyterminal propeptide of type-I procollagen (PICP), tissue inhibitor of metalloproteinases (TIMP-1), and matrix metallopeptidase-9 (MMP-9), as well as several micro-RNA profiles and orexin A (the ligand for the hypocretin receptor) [22, 23]. A role may be for blood biomarkers in the evaluation of antihypertensive treatment [24, 25].

Although circulating biochemical markers may offer the advantage of wide availability and low cost, they do not have the sensitivity of imaging biomarkers and therefore, more data are still needed before the inclusion of the above biomarkers in the routine evaluation of cardiac remodeling will be recommended.

Imaging biomarkers for cardiac remodeling evaluation

Cardiac imaging is the gold standard for assessing cardiac remodeling. Serial echocardiographic evaluation is the most common diagnostic modality, used in clinical practice and has been widely val-

idated in most clinical trials. A reduction in LV end- systolic volume (LVESV) is the most commonly used index of reverse remodeling in echocardiographic studies because it provides both anatomical and functional information. Strain imaging is relatively independent of LV volume and shape and is more sensitive than LVEF in detecting systolic dysfunction. In other studies, radial dys-synchrony was associated with significant improvements in LVESV and clinical outcomes following cardiac re-synchronization treatment (CRT), independently of QRS duration or morphology [26]. Three-dimensional (3D) echocardiography and 3D speckle tracking echocardiography allow for fast quantification of global LV dys-synchrony and are associated with a positive CRT response and reverse remodeling after CRT [27].

Compared to echocardiography, CMR has better spatial resolution, higher reproducibility and independence from operator expertise and patient's acoustic window. Furthermore, it can provide valuable information regarding the presence and extent of myocardial replacement fibrosis, presented as late gadolinium enhancement (LGE) [28]. LGE is inversely related to reverse remodeling [29–31]. In a study of 58 patients with dilated cardiomyopathy, the absence of LGE predicted improved LV dimensions and function, independently of the severity of pre-existing LV dysfunction [32]. Other studies showed high specificity and positive predictive value of LGE absence in predicting reverse remodeling, associated with better prognosis [33]. T1 mapping is a useful new imaging index to noninvasively quantify extracellular volume and diffuse myocardial fibrosis and is a prognostic index in patients with inflammation and HFrEF [34–38]. Furthermore, the native T1 mapping technique has the potential to discriminate myocardial fibrotic changes in athletes in comparison to non-athletes [39]. The native T1 mapping seems to be a safe and easily measured index to evaluate cardiac hypertrophy in athletes, because it does not need contrast agents and allows for easy evaluation of myocardial remodeling [39]. Finally, native T1 was the strongest discriminator between patients with myocardial hypertrophy and healthy controls. Significantly increased T2 mapping was found in chronic kidney disease (CKD) and to a lesser extent in hypertension, but not in hypertrophic cardiomyopathy (HCM). Together with a strong interrelationship between native T1 and T2 in CKD and less so in hypertension, this finding suggests a prominent role of intramyocardial fluid in changes of native T1 in the conditions with primarily LV pressure and volume overload. On the contrary, weak relationship between native T1 and T2 in HCM suggests that the predominant cause of changes in native T1 is mediated through diffuse myocardial fibrosis [40, 41].

Furthermore, in patients with HHD, CMR-derived indices of myocardial fibrosis and function can identify preclinical cardiac dysfunction. Molecular biomarkers of fibrosis are marginally associated with myocardial strain, but not with the extension of CMR-measured cardiac fibrosis [42].

Heart and brain interaction

There is a complex interaction between the cardiovascular (CV) and central nervous systems. Any lesion of one organ may lead to dysfunction of the other. Furthermore, both organs are affected by the same CV risk factors, including hypertension, diabetes mellitus, dyslipidemia and are prone to ischemia, due to atherosclerotic or thrombotic lesions, ultimately leading to acute or chronic organ dysfunction. The heart and the brain are linked through multiple communication signals and mutual interaction, finally leading to combined progression or remission of disease processes [43].

In patients with known CAD, myocardial infarction (MI) was associated with increased risk of Alzheimer dementia [43–45]. Furthermore, acute MI triggers both local and systemic inflammation, which increases atherosclerosis, activates the autonomic nervous system, and contributes to LV remodeling [46, 47]. The Framingham study reported that the stroke incidence was more than double in CAD, more than triple in hypertension, 4-fold and 5-fold increased in HF and atrial fibrillation, respectively [48].

HF is also associated with elevated levels of systemic pro-inflammatory cytokines, which are associated with future cardiac events [48, 49]. On the other hand, the brain is rich in microglia, which is the main nervous immune response to local or systemic damage [50]. Neuro-inflammation is the leading cause of Alzheimer disease. Microglia is activated by amyloid and has neurotoxic effects, which further increase the inflammatory process and promote amyloid deposition [51]. The role of neuro-inflammation in the development of Alzheimer disease has been already recognized. Although activation of microglia is an immune response to misfolded proteins, such as beta-amyloid, it is also necessary for clearance of neuro-inflammation and may cause neuro-toxicity and increased neuro-degeneration [51]. The biphasic pattern of neuro-inflammation, with peaks in early acute and late chronic stages of cardiac damage, shows similarity to clinical observations of the biphasic pattern of initial mild cognitive impairment and late advanced Alzheimer disease [52, 53]. Finally, the recurrent neuro-inflammation in HF may be related to impaired cerebral blood flow and elevated pro-inflammatory cytokines [54–56].

Similarly, blood pressure alterations usually lead to changes in brain perfusion/metabolism. The capacity of the neurovascular territories to respond to perfusion variation is referred to as dynamic autoregulation and/or brain vascular reserve. Hypertension with concurrent endothelial dysfunction decreases the brain's ability for dynamic autoregulation [57] and upgrade of blood flow to meet with cognitive demands. This reduced capacity may contribute to small vessel disease and diminished clearance of amyloid β A4 protein from the brain. The combination of advanced age with hypertension provides the ideal background for multiple patho-physiological pathways leading to cognitive decline and dementia [58]. Furthermore, hypertension accelerates arteriosclerotic changes in the brain leading to dysfunction of cerebral vasculature [58] with consequent perfusion reduction [58], which can cause cerebral infarction, clinically expressed as vascular cognitive dysfunction.

Heart and kidney interaction

Cardiac disease leads to a progressive decline of renal function and final to cardio-renal syndrome (CRS) [59]. It affects the kidney through hemodynamic, neuro-hormonal, inflammatory activation and diuretic treatment. Even a modest decrease of renal function in patients with cardiac disease may lead to increased mortality [59].

Hypertension is prevalent in ≈ 30 % of patients with chronic kidney disease (CKD) [60] and represents a risk factor for the develop-

ment of chronic kidney disease (CKD), which can be worsened by sodium/water retention, renin-angiotensin system (RAAS), sympathetic nervous system activation and/or endothelial dysfunction. The prevalence of drug-resistant hypertension is increased in patients with CKD, which is associated with an impaired CV prognosis in patients with resistant hypertension [61].

Tissue fibrosis occurs in both heart and kidneys as a result of chronic diseases, including hypertension [62]. Many mediators including neurohormones (sympathetic nervous system, renin-angiotensin system, endothelin and arginine vasopressin), local cell signaling via immune and satellite cells (interleukins, tumor necrosis factor-α, connective tissue growth factor, lysyl oxidase homologue 2, NADPH oxidase, and vascular epithelial growth factor) are responsible for this process [63, 64].

Myocardial remodeling after hypertension promotes the secretion of extracellular matrix proteins by myofibroblasts, leading to cardiac fibrosis and preserved myocardial structure/function. However, fibrosis leads to cardiac dilatation, cardiomyocyte hypertrophy, apoptosis and HF [65]. In the kidney, tubulointerstitial fibrosis/dysfunction may result by the differentiation of tubular epithelial cells to myofibroblasts toward an epithelial-mesenchymal transition phenotype, leading to a fibroblastic phenotype, with increased extracellular matrix synthesis. Aldosterone may trigger a cascade of mechanisms contributing to fibrosis of heart, blood vessels, kidneys, and, finally, development of CRS [65].

On the other side, in chronic kidney disease (CKD), the decreased glomerular filtration rate is associated with diffuse deposition of fibrotic tissue in the myocardial interstitium leading to myocardial interstitial fibrosis (MIF)] and loss of cardiac function. MIF is produced by cardiac fibroblast-mediated alterations in the turnover of fibrillary collagen. This leads to the excessive synthesis and deposition of stiff collagen fibers. The accumulation of stiff fibrotic tissue further contributes to the development of HF. There is increasing evidence supporting that there are mechanisms acting along the different stages of CKD that may alter fibroblasts and collagen turnover in the heart. Therefore, focusing on MIF, we may identify fibrosis-related blood or imaging biomarkers that could potentially lead to a better preventive or therapeutic approach of CR in patients with CKD [66].

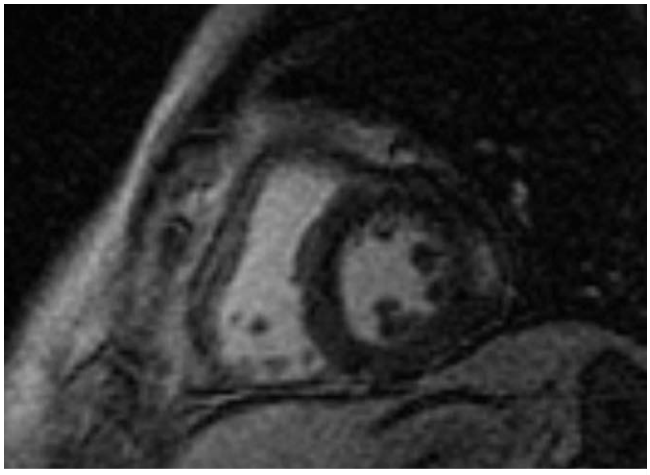
The reason for a combined magnetic resonance imaging of brain, heart, and kidney

It is clear that there is not only cardiac remodeling during the course of systemic hypertension, but also “remodeling” of other vital organs, such as the brain and kidneys. Therefore, it will be more accurate if we discuss about “hypertensive modeling” involving brain, heart and kidney, instead of isolated cardiac remodeling. The close interaction of these organs strongly supports the proposal of their simultaneous assessment to identify the early, silent lesions of “hypertensive remodeling”. In this context, magnetic resonance imaging (MRI) is the ideal imaging modality that can provide information about these organs noninvasively and without radiation. For this purpose, we propose a combined protocol including heart, brain and kidney assessment, using MRI. The protocol should include all necessary indices for the evaluation of “hypertensive remodeling” in these 3 organs and should be performed at a reasonable time, which should not exceed one hour to remain patient-friendly. Furthermore, a combined protocol may offer “all in one examination” and save time. Finally, the amount of contrast agent used will be reduced, because brain-heart post contrast MRI will be performed in the same examination after 1 injection.

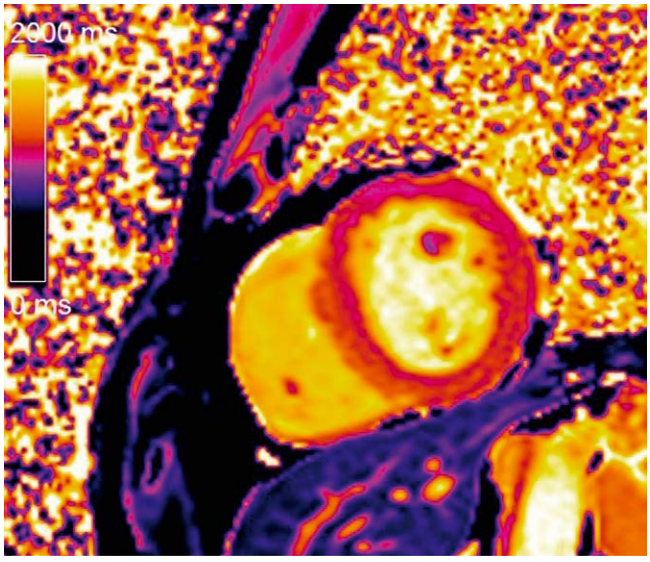
The CMR protocol should include standard steady-state free-precession (SSFP) sequence for bi-ventricular function evaluation, inversion recovery sequence, 10–15 minutes after IV injection of contrast agent to acquire late gadolinium enhanced (LGE) images for detection of replacement fibrosis (▶ **Fig. 1**). In addition, T1-mapping measurements should be performed using a modified Look-Locker inversion recovery (MOLLI) sequence, with a 3(3)5 scheme on 3 representative short-axis positions before (native) and 15 minutes after contrast-medium administration (post-contrast) (▶ **Fig. 2**). T2-mapping is performed on 3 corresponding LV short-axis slices using a black-blood prepared, navigator-gated, free-breathing hybrid gradient (echo planar imaging) and spin-echo multiecho sequence [67]. Finally, T2 mapping can identify a specific group of hypertensions with myocardial edema [40].

A standard MRI protocol for brain evaluation should include the following measurements [67]:

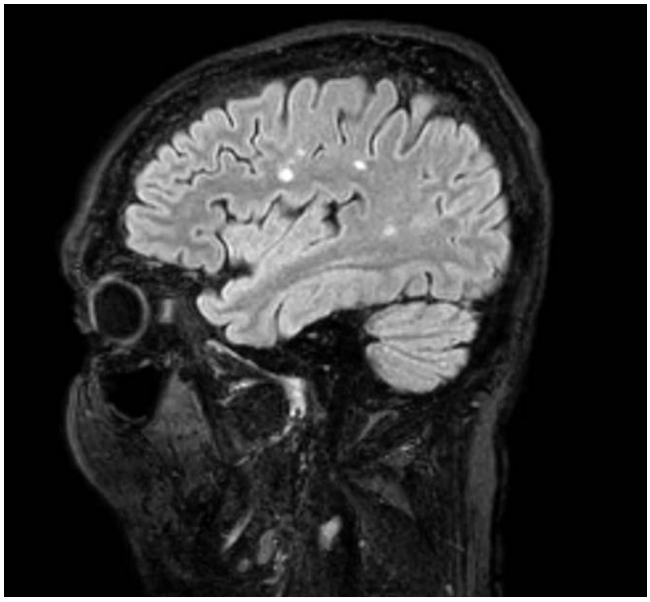
a) Spin-echo T1- and T2-weighted imaging where only fat is bright, while in T2 imaging both fat and water are bright. FLAIR imaging is also similar to T2 and can be used to identify subtle oedema after a stroke (▶ **Fig. 3**).
b) Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) With DWI scans, ischemia can be visualized within minutes of its development, because DWI has high signal in early ischemia, but lowers after several weeks. In contrast ADC has low signal at first, but the signal increases over several weeks and stays high.
c) Susceptibility-weighted (SWI) imaging for the identification of small amounts of hemorrhage/blood products or calcium, both of which may be undetectable on other MRI sequences.



▶ **Fig. 1** Short axis inversion recovery image showing intramyocardial fibrosis in a patient with hypertension and normal coronary arteries.



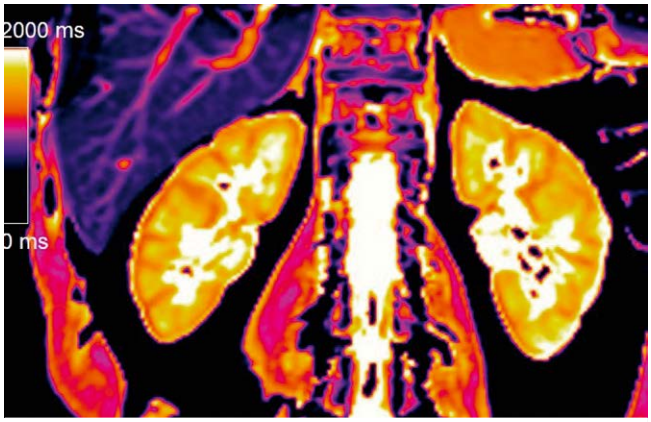
▶ **Fig. 2** Cardiac native T1 mapping showing evidence of diffuse myocardial fibrosis in a patient with hypertension.



▶ **Fig. 3** Brain FLAIR image showing WMH in a patient with hypertension and cardiac remodeling.

d) Time-of-flight (TOF) MR angiography. It is a technique for routine assessment of stenosis and occlusion of intracranial blood vessels.
e) Contrast-enhanced T1-weighted imaging is superior at measuring and assessing tumors. Furthermore, MRI images with contrast are clearer and of better quality than the images without contrast.

The usual MRI protocol for evaluation of the kidney includes: a) Coronal T2-weighted half Fourier single-shot turbo spin echo sequence (HASTE), b) Axial T2-weighted turbo spin echo sequence with fat suppression, c) Axial T1-weighted gradient echo sequence to assess various types of solid renal lesions, d) Axial T1-weighted gradient echo sequence for dynamic imaging for lesion characterization, and e) Coronal 3D fast gradient echo with fat suppression immediately after the dynamic series for delayed contrast-enhanced images for the analysis of tumor/thrombus



▶ **Fig. 4** Kidneys native T1 mapping showing evidence of fibrosis in a patient with hypertension.

Recently, a systematic review, initiated by the European Cooperation in Science and Technology Action Magnetic Resonance Imaging Biomarkers for Chronic Kidney Disease (PARENCHIMA), focuses on potential clinical applications of magnetic resonance imaging in renal nontumor disease using magnetic resonance relaxometry (MRR), specifically, the measurement of the independent quantitative magnetic resonance relaxation times T_1 and T_2 at 1.5 and 3 Tesla (T), respectively. Healthy subjects show a distinguishable cortico-medullary differentiation (CMD) in T_1 and a slight CMD in T_2. Increased cortical T_1 values that is, reduced T1 CMD, were reported in acute allograft rejection (AAR) and diminished T_1 CMD in chronic allograft rejection. Although, these findings could not differentiate AAR from acute tubular necrosis and cyclosporine nephrotoxicity, a recent quantitative study showed in renal transplants a direct correlation between fibrosis and T_1 CMD. Additionally, various renal diseases, including renal transplants, showed a moderate to strong correlation between T_1 CMD and renal function. Renal MRR is also sensitive to renal perfusion, ischemia/oxygenation, edema, fibrosis, hydration and comorbidities, which reduce specificity. Therefore, standardization in patient preparation and acquisition protocols are needed in order to include these indices in hypertensive patients' routine evaluation [68].

In our protocol, we suggest that the evaluation of kidneys should be performed using a native T1 protocol. T1 protocol is acquired using a modified Look-Locker inversion recovery (MOLLI) sequence. According to the literature, if the ratio of native T1 mapping values of kidney cortex against kidney medulla is > 0.7, this is an index of kidney fibrosis and has a direct correlation with histologic findings [69] (▶ **Fig. 4**). This targeted protocol, although it does not provide information regarding all types of renal abnormalities, it is reliable to assess kidney fibrosis [69].

Conclusions

Hypertension is the most common causative factor of cardiac remodeling, which, in turn can influence brain and kidney functions. Currently, the role of blood biomarkers as indices of cardiac remodeling remains unclear. In contrast, cardiac imaging is a valuable noninvasive tool to assess cardiac remodeling. In this context, we propose a combined heart, brain, and kidney protocol using MRI to identify in the same examination cardiac, brain, and kidney remodeling in hypertensive patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling-concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. On behalf of an international forum on cardiac remodeling. J Am Coll Cardiol 2000; 35: 569–582

[2] Biernacka A, Frangogiannis NG. Aging and cardiac fibrosis. Aging Dis 2011; 2: 158–173

[3] Brilla CG, Murphy RL, Smits JF et al. The concept of cardioreparation: Part 1. Pathophysiology of remodelling. J Cardiovasc Risk 1996; 3: 281–285

[4] Santulli G, Iaccarino G. Adrenergic signaling in heart failure and cardiovascular aging. Maturitas 2016; 93: 65–72

[5] Goldberg LI, Bloodwell RD, Braunwald E et al. The direct effects of norepinephrine, epinephrine, and methoxamine on myocardial contractile force in man. Circulation 1960; 22: 1125–1132

[6] Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014; 114: 1004–1021

[7] Drazner MH. The progression of hypertensive heart disease. Circulation 2011; 123: 327–334

[8] Frey N, Olson EN. Cardiac hypertrophy: the good, the bad, and the ugly. Annu Rev Physiol 2003; 65: 45–79

[9] Creemers EE, Pinto YM. Molecular mechanisms that control interstitial fibrosis in the pressure-overloaded heart. Cardiovasc Res 2011; 89: 265–267

[10] González A, Ravassa S, López B et al. Myocardial remodeling in hypertension. Hypertension 2018; 72: 549–558

[11] Bhardwaj A, Rehman SU, Mohammed A et al. Design and methods of the Pro-B type natriuretic peptide outpatient tailored chronic heart failure therapy (PROTECT) study. Am Heart J 2010; 159: 532–538

[12] Januzzi JL Jr., Rehman SU, Mohammed AA et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients. JACC with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011; 58: 1881–1889

[13] Daubert MA, Adams KF, Yow E et al. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in HFrEF. J Am Coll Cardiol HF 2019; 7: 158–168

[14] Fruhwald FM, Fahrleitner-Pammer A, Berger R et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. Eur Heart J 2007; 28: 1592–1597

[15] Gaggin HK, Szymonifka J, Bhardwaj A et al. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. J Am Coll Cardiol HF 2014; 2: 65–72

[16] Pichler G, Martínez F, Calaforra O et al. Cardiac morphology measured with magnetic resonance imaging is related to biomarkers of myomarkers of myocardial stretch and injury in hypertensive heart disease. J Hypertension 2019; 37: p e4

[17] Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drugs Discov 2008; 7: 827–840

[18] Lupon J, Sanders-van Wijk S, Januzzi JL et al. Prediction of survival and magnitude of reverse remodeling using the ST2-R2 score in heart failure: a multicenter study. Int J Cardiol 2016; 204: 242–247

[19] Solomon SD, Skali H, Anavekar NS et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 2005; 111: 3411–3419

[20] Hogas S, Bilha SC, Branisteanu D et al. Potential novel biomarkers of cardiovascular dysfunction and disease: Cardiotrophin-1, adipokines and galectin-3. Arch Med Sci 2017; 13: 897–913

[21] Dong T, Li H, Wang S et al. Efficacy evaluation of serum galectin-3 in hypertension complicated with diastolic dysfunction. Exp Ther Med 2020; 19: 147–152

[22] González A, López B, Ravassa S et al. Biochemical markers of myocardial remodelling in hypertensive heart disease. Cardiovasc Res 2009; 81: 509–518

[23] Peters LJF, Biessen EAL, Hohl M et al. Small things matter: relevance of microRNAs in cardiovascular disease. Front Physiol 2020; 11: 793

[24] Dhingra R, Pencina MJ, Schrader P et al. Relations of matrix remodeling biomarkers to blood pressure progression and incidence of hypertension in the community. Circulation 2009; 119: 1101–1107

[25] Neumann JT, Schwerg M, Dörr O et al. Biomarker response and therapy prediction in renal denervation therapy – the role of MR-proadrenomedullin in a multicenter approach. Biomarkers 2017; 22: 225–231

[26] Marsan NA, Breithardt OA, Delgado V et al. Predictinresponse to CRT. The value of two- and three-dimensional echocardiography. Europace 2008; 10: iii73–iii79

[27] Barison A, Grigoratos C, Todiere G et al. Myocardial interstitial remodelling in non-ischaemic dilated cardiomyopathy: insights from cardiovascular magnetic resonance. Heart Fail Rev 2015; 20: 731–749

[28] Ishii S, Inomata T, Fujita T et al. Clinical significance of endomyocardial biopsy in conjunction with cardiac magnetic resonance imaging to predict left ventricular reverse remodeling in idiopathic dilated cardiomyopathy. Heart Vessels 2016; 31: 1960–1968

[29] Chimura M, Onishi T, Tsukishiro Y et al. Longitudinal strain combined with delayed-enhancement magnetic resonance improves risk stratification in patients with dilated cardiomyopathy. Heart 2017; 103: 679–686

[30] Barison A, Aimo A, Ortalda A et al. Late gadolinium enhancement as a predictor of functional recovery, need for defibrillator implantation and prognosis in non-ischemic dilated cardiomyopathy. Int J Cardiol 2018; 250: 195–200

[31] Masci PG, Schuurman R, Andrea B et al. Myocardial fibrosis as a key determinant of left ventricular remodeling in idiopathic dilated cardiomyopathy: a contrast-enhanced cardiovascular magnetic study. Circ Cardiovasc Imaging 2013; 6: 790–799

[32] Cojan-Minzat BO, Zlibut A, Agoston-Coldea L. Non-ischemic dilated cardiomyopathy and cardiac fibrosis. Heart Fail Rev 2021; 26: 1081–1101

[33] Azuma M, Kato S, Sekii R et al. Extracellular volume fraction by T1 mapping predicts improvement of left ventricular ejection fraction after catheter ablation in patients with non-ischemic dilated cardiomyopathy and atrial fibrillation. Int J Cardiovasc Imaging 2021; 37: 2535–2543

[34] Mavrogeni S, Apostolou D, Argyriou P et al. T1 and T2 mapping in cardiology: “mapping the obscure object of desire”. Cardiology 2017; 138: 207–217

[35] Won S, Davies-Venn C, Liu S et al. Noninvasive imaging of myocardial extracellular matrix for assessment of fibrosis. Curr Opin Cardiol 2013; 28: 282–289

[36] Ferreira VM, Piechnik SK, Dall’Armellina E et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2012; 14(1): 42

[37] Mavrogeni SI, Sfikakis PP, Markousis-Mavrogenis G et al. Cardiovascular magnetic resonance imaging pattern in patients with autoimmune rheumatic diseases and ventricular tachycardia with preserved ejection fraction. Int J Cardiol 2019; 284: 105–109

[38] Graham-Brown MP, McCann GP. T1 Mapping in athletes: a novel tool to differentiate physiological adaptation from pathology? Circ Cardiovasc Imaging 2016; 9: e004706

[39] Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M et al. Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol 2010; 61: 509–521

[40] Arcari L, Hinojar R, Engel J et al. Native T1 and T2 provide distinctive signatures in hypertrophic cardiac conditions – Comparison of uremic, hypertensive and hypertrophic cardiomyopathy. Int J Cardiol 2020; 306: 102–108

[41] Hinojar R, Varma N, Child N et al. T1 Mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the international T1 multicenter cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2015; 8: e003285

[42] Pan JA, Michaëlsson E, Shaw PW et al. Extracellular volume by cardiac magnetic resonance is associated with biomarkers of inflammation in hypertensive heart disease. J Hypertens 2019; 37: 65–72

[43] Ikram MA, van Oijen M, de Jong FJ et al. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. Stroke 2008; 39: 1421–1426

[44] Beeri MS, Rapp M, Silverman JM et al. Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. Neurology 2006; 66: 1399–1404

[45] Dutta P, Courties G, Wei Y et al. Myocardial infarction accelerates atherosclerosis. Nature 2012; 487: 325–329

[46] Westman PC, Lipinski MJ, Luger D et al. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. J Am Coll Cardiol 2016; 67: 2050–2060

[47] Verdecchia P, Porcellati C, Reboldi G et al. Left ventricular hypertrophy as an independent predictor of acute cerebrovascular events in essential hypertension. Circulation 2001; 104: 2039–2044

[48] Dick SA, Epelman S. Chronic heart failure and inflammation: what do we really know? Circ Res 2016; 119: 159–176

[49] Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res 2015; 116: 1254–1268

[50] Rivest S. Regulation of innate immune responses in the brain. Nat Rev Immunol 2009; 9: 429–439

[51] Cagnin A, Brooks DJ, Kennedy AM et al. In vivo measurement of activated microglia in dementia. Lancet 2001; 358: 461–467

[52] Jacobs AH, Tavitian B. INMiND Consortium Noninvasive molecular imaging of neuroinflammation. J Cereb Blood Flow Metab 2012; 32: 1393–1415

[53] Fan Z, Brooks DJ, Okello A et al. An early and late peak in microglial activation in Alzheimer’s disease trajectory. Brain 2017; 140: 792–803

[54] Fan Z, Okello AA, Brooks DJ et al. Longitudinal influence of microglial activation and amyloid on neuronal function in Alzheimer’s disease. Brain 2015; 138: 3685–3698

[55] Meissner A, Visanji NP, Momen MA et al. Tumor necrosis factor-alpha underlies loss of cortical dendritic spine density in a mouse model of congestive heart failure. J Am Heart Assoc 2015; 4: e001920

[56] Shi P, Diez-Freire C, Jun JY et al. Brain microglial cytokines in neurogenic hypertension. Hypertension 2010; 56: 297–303

[57] Carnevale D, Lembo CD. Hypertension and cerebrovascular dysfunction: Acute and chronic brain pathological alterations. High Blood Press Cardiovasc Prev 2012; 17: 191–200

[58] Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. Circ Res 2019; 124: 1025–1044

[59] Zannad F, Rossignol P. Cardiorenal syndrome revisited. Circulation 2018; 138: 929–944

[60] Rossignol P, Massy ZA, Azizi M et al. ERA-EDTA EURECA-m working group; red de investigación renal (REDINREN) network; cardiovascular and renal clinical trialists (F-CRIN INI-CRCT) network. The double challenge of resistant hypertension and chronic kidney disease. Lancet 2015; 386: 1588–1598

[61] Travers JG, Kamal FA, Robbins J et al. Cardiac fibrosis: the fibroblast awakens. Circ Res 2016; 118: 1021–1040

[62] McCullough PA. Cardiorenal syndromes: pathophysiology to prevention. Int J Nephrol 2010; 2011: 762590

[63] Tampe D, Zeisberg M. Potential approaches to reverse or repair renal fibrosis. Nat Rev Nephrol 2014; 10226–10237

[64] Cruz DN, Schmidt-Ott KM, Vescovo G et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol 2013; 182: 117–136

[65] Travers JG, Kamal FA, Robbins J et al. Cardiac fibrosis: the fibroblast awakens. Circ Res 2016; 118: 1021–1040

[66] Romero-González G, González A, López B et al. Heart failure in chronic kidney disease: the emerging role of myocardial fibrosis. Nephrol Dial Transplant 2020; gfaa284. doi:10.1093/ndt/gfaa284 Epub ahead of print

[67] Markousis-Mavrogenis G, Mitsikostas DD, Koutsogeorgopoulou L et al. Combined brain-heart magnetic resonance imaging in autoimmune rheumatic disease patients with Cardiac symptoms: hypothesis generating insights from a cross-sectional study. J Clin Med 2020; 9: 447

[68] Wolf M, de Boer A, Sharma K et al. Magnetic resonance imaging T1- and T2-mapping to assess renal structure and function: a systematic review and statement paper. Nephrol Dial Transplant 2018; 33: ii41–ii50

[69] Friedli I, Crowe LA, Berchtold L et al. New magnetic resonance imaging index for renal fibrosis assessment: a comparison between diffusion-weighted imaging and T1 mapping with histological validation. Sci Rep 2016; 6: 30088