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 LVEV, 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 HF/EF, 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-
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 pathophysiological pathways leading to cognitive decline and dementia [58]. Furthermore, hypertension accelerates atherosclerotic 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 fibrillar tissue in the myocardial interstitium leading to myoccardial 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 fibroitic 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 remodeling” 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.
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.

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 T1 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
