State of the art: advanced imaging of the right ventricle and pulmonary circulation in humans (2013 Grover Conference series)

Mariëlle C. van de Veerdonk,[1] J. Tim Marcus,[2] Harm-Jan Bogaard,[1] Anton Vonk Noordegraaf[1]

[1]Pulmonary Diseases, Institute for Cardiovascular Research (ICaR-VU), VU University Medical Center, Amsterdam, The Netherlands; [2]Physics and Medical Technology, ICaR-VU, VU University Medical Center, Amsterdam, The Netherlands

Abstract: Pulmonary arterial hypertension (PAH) is a progressive disease characterized by remodeling and vasoconstriction of the pulmonary vasculature, ultimately leading to right ventricular (RV) failure and death. Recent developments in echocardiography, cardiovascular magnetic resonance imaging, computed tomography, and positron emission tomography allow advanced, noninvasive, in vivo assessment of the RV and have contributed to the identification of risk factors, prognostic factors, and monitoring of therapeutic responses in patients with PAH. Although far from reaching its future potential, these techniques have not only provided global RV assessment but also allowed evaluation of changes in cellular and molecular tissue processes, such as metabolism, oxygen balance and ischemia, angiogenesis, and apoptosis. Integrated application of these techniques could provide full insights into the different pathophysiological aspects of a failing RV in the setting of PAH. Recent advances in hybrid imaging have implemented simultaneous measurements of myocardial and vascular interactions and will be one of the most important potential future developments.

Keywords: pulmonary arterial hypertension, right ventricle, cardiovascular magnetic resonance imaging, echocardiography, positron emission tomography.

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INTRODUCTION

Historically, the role of the right ventricle (RV) was considered of minor relevance in the maintenance of adequate blood flow and therefore has been largely understudied.[1] Currently, the RV is receiving increased attention, because the prognostic significance of RV dysfunction is now recognized in pulmonary hypertension (PH), left ventricular (LV) failure, acute respiratory distress syndrome, and sepsis.[2] In pulmonary arterial hypertension (PAH), a progressive disease characterized by pulmonary vascular remodeling leading to chronic pressure overload, RV failure is often the cause of death.[3,4] However, RV dysfunction is not simply determined by a chronically elevated afterload.[5-7] It has been recognized that patients with PAH differ in their tendency to develop RV failure, with some patients developing early RV failure and others showing an adapted RV that tolerates the same hemodynamics on a long-term basis.[8-10] The underlying mechanisms behind the transition from RV adaptation to decompensation are only partially understood. Remarkably, a patient with RV failure can completely recover after lung transplantation.[11] Insights into the pathophysiology of RV failure and its relation to the pulmonary circulation are relevant for diagnosis, risk stratification, and management of patients with PAH.

Over the previous decades, advanced, noninvasive imaging techniques have emerged. Recent developments in echocardiography, cardiovascular magnetic resonance imaging (CMR), computed tomography (CT), and positron emission tomography (PET) not only allow for global RV assessment but can also detect changes on a regional and molecular level. These techniques may help considerably to better understand the contributing pathophysiological factors in the development of RV failure. Here, we provide an overview of advanced, noninvasive assessment of the RV, review new imaging modalities, and assess the potential value of combining imaging techniques to improve our

Address correspondence to Dr. Anton Vonk Noordegraaf, Department of Pulmonary Diseases, VU University Medical Center, 1081 HV Amsterdam, Netherlands. E-mail: a.vonk@vumc.nl.

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insights into the mechanisms of RV adaptation and failure in PAH.

MORPHOLOGICAL AND FUNCTIONAL IMAGING

RV hypertrophy and dilatation

CMR has become the gold standard for quantification of RV mass, volumes, and function and provides high-resolution imaging without requirement of geometric assumptions and ionizing radiation.[12] Integrated assessment of multiple CMR parameters may provide insights into RV remodeling processes. Using combined measurements of RV pressures and CMR analyses of RV mass and volumes, ventricular wall stress can be calculated according to the law of Laplace (i.e., wall stress = intraluminal pressure times chamber internal radius, divided by wall thickness).[13] Elevated pressures result in increased ventricular wall stress, which is detrimental for the RV in the long run.[14,15] RV hypertrophy is initially considered a favorable remodeling mechanism by reducing wall stress and improving pumping effectiveness. In PAH, RV mass, wall thickness, and the ventricular mass index (i.e., ratio of RV mass to LV mass) measured by CMR or multidetector computed tomography (MDCT) were increased and moderately related to pulmonary pressures.[16-19] However, in PAH, RV mass is, on average, 2.5-fold increased, which might be insufficient to compensate for an often fourfold increase in pulmonary pressure. In line with these findings, Simon et al.[20] demonstrated regional heterogeneity in RV structural remodeling, and it was shown that, although RV wall thickness increases during the course of disease, it remained insufficient to normalize the RV wall stress. These results might explain the limited value of RV mass for predicting mortality in patients with idiopathic PAH.[21] Moreover, in patients with scleroderma and PAH, elevated RV mass was associated with increased mortality.[17] An increase in RV mass is therefore not only a favorable physiologic adaptation mechanism and may be associated with maladaptive changes.

Although RV dilatation may aid in sustaining cardiac output via the Frank-Starling mechanism, at the same time, it contributes to elevated wall stress. An increased RV end-diastolic volume and progressive dilatation during follow-up assessed by CMR were among the strongest predictors of mortality in PAH.[21,22]

Although readily available in clinical practice, volumetric assessment can be less reliably performed by two-dimensional echocardiography because of the difficulty in visualizing the RV anterior wall and infundibulum. This explains the variable correlations between volumetric echocardiographic and CMR measures.[2,23,24] Three-dimensional echocardiography is a promising technique and showed better agreement with CMR compared with a two-dimensional assessment; nevertheless, it resulted in underestimations of RV volumes and function, particularly in a dilated RV.[25] Future advances can be expected to allow a better image acquisition of wide-angle windows to obtain data from the entire RV with higher temporal and spatial resolution.

Global RV function

Stroke volume and RV ejection fraction measured by CMR are the most commonly used parameters to evaluate global systolic RV function[2] and contain therapeutic and prognostic information in PAH.[6,21,22,26] Only a few studies have assessed RV diastolic dysfunction, and few data exist on their accuracy.[27,28] Although these functional parameters are dependent on preload and afterload and therefore do not fully characterize intrinsic RV function,[15,29] load-independent measures can provide new insights on intrinsic cardiac properties or direct cardiac treatment effects. RV end-systolic elastance (Ees) is accepted as a load-independent measure of intrinsic myocardial contractility. Although the classical determination of Ees requires multiple pressure-volume loops and dangerous, invasive interventions, a single-beat method has been validated that enables estimation of Ees using a simpler approach that can be obtained by right heart catheterization and assessment of a RV pressure-volume relationship during a single heartbeat, without invasive mediations. Using this method, arterial elastance (Ea) as a measure of RV afterload can also be determined.[30-32] The ratio of Ees to Ea represents efficiency of the ventriculo-arterial coupling. In addition, CMR approaches have been developed to estimate Ees noninvasively.[33,34] Paradoxically, it has been found that RV contractility is increased in patients with PAH, whereas global measures of RV systolic function, such as RV ejection fraction and stroke volume, are decreased.[35] These findings might be explained by the fact that, although the RV compensates for the increased afterload by hypercontractility, this was insufficient, leading to ventriculo-arterial uncoupling. Future studies are required to validate and evaluate the clinical relevance of contractility measures. Recently, Rain and coworkers[35] have applied and validated the single-beat method to determine load-independent RV diastolic stiffness, which was found to be significantly increased in PAH and was related to disease severity.

Regional RV function and strain

The normal RV consists of transverse-oriented superficial muscle fibers and more longitudinally aligned deep muscle fibers, resulting in a primarily bellows-like or peristal-

tic contraction pattern.[36-39] RV longitudinal shortening (tricuspid annular plane excursion [TAPSE]) and transverse shortening provide clinical relevant measures that are correlated with global RV function.[22,40,41] Although the determination of global measures of RV function is relative time consuming, these measures are simpler to obtain. Mauritz et al.[22] showed that both transverse and longitudinal shortening were valuable parameters and that, in particular, a progressive decrease in RV transverse wall motion is associated with end-stage RV disease.

Regional RV function, as reflected by local myocardial deformation, can be estimated by segmental strain (relative amount of deformation) and strain rate (velocity of deformation) using echocardiographic tissue Doppler velocity imaging (TDI) or two-dimensional speckle tracking. TDI measures do not rely on geometric assumptions but are one-dimensional and angle dependent.[42] Speckle tracking is a more recently developed method that can reliably determine myocardial deformation. However, it has limited reproducibility and loss of speckles due to motion outside the imaging plane.[43] According to Hooke's law (i.e., forces and deformation are linked to elasticity[44]), myocardial deformation is mainly influenced by intrinsic contractility (active forces), cavity pressures, geometry and neighboring segment interaction (passive forces or wall stress), and tissue elasticity (fiber structure and fibrosis), of which contractility is the most important.[45] In healthy animals, Jamal et al.[46] showed by TDI that longitudinal strain and strain rate provided complementary information in which strain is a reflection of stroke volume and strain rate is a reflection of load-independent contractility. Myocardial acceleration during isovolumic contraction is another measure of load-independent RV function in healthy animals, but validation in PAH is required.[47] In patients with PAH, a reduced longitudinal strain has been demonstrated, with the most severe impairments in patients with RV failure.[48-54] Regional heterogeneity was an important feature of a dysfunctional RV in which the apical region is the most affected.[53] Furthermore, RV longitudinal strain and strain rate are independent predictors of survival.[48,55] However, longitudinal strain describes only one aspect of myocardial deformation and does not allow estimation in the complex three-dimensional RV contraction pattern. Circumferential and radial strain are more difficult to study by two-dimensional speckle tracking and TDI, respectively. Recent three-dimensional speckle tracking methods have been developed that allow a more complete and accurate assessment of myocardial deformation in the LV.[56] Studies have not yet been performed in the RV. Intramyocardial motion can also be determined by CMR techniques in which the myocardium is initially "tagged" by a line or grid pattern at end-diastole that deforms during contraction.[57] The deformation of these "tagging" lines can be quantified. CMR tagging techniques are currently considered the reference for RV strain analysis and allow assessment in multiple directions, but their clinical application is limited because of complex and time-consuming analyses. It has been found in patients with PH that both longitudinal and circumferential shortening were reduced to a similar level.[58] Moreover, it was recently illustrated that, although global RV function was intact, regional longitudinal wall deformation was already impaired, implying that this could be a sensitive measure to detect early RV dysfunction in PAH.[59] In a systemic RV, circumferential exceeds longitudinal wall deformation, which is comparable to the normal LV.[60]

In healthy hearts, a significant proportion of RV output is attributable to the interventricular septum (IVS)[61,62] and LV contraction.[63-65] Therefore, both intra- and interventricular dyssynchrony are important aspects of RV function. Echocardiography demonstrated a longer delay in the time to peak strain between the IVS and RV lateral wall and a delay in time to peak strain between the LV and RV lateral walls in patients with PAH compared with controls.[66,67] The delay in LV-RV peak shortening is the result of a prolonged RV contraction time that even continues after pulmonary valve closure and is related to leftward IVS bulging, LV underfilling, and a lowered stroke volume (Fig. 1).[68,69]

METABOLIC IMAGING

In patients with a hypertrophic or dilated LV cardiomyopathy, PET imaging has shown that the predominant metabolic substrate of the LV has switched from fatty acids to glucose metabolism, thereby preserving the adenosine triphosphate supply for force generation.[70-72] In line with these findings, single-photon emission tomography (SPECT) imaging has demonstrated that, in the hypertrophied RV of patients with PH, myocardial fatty acid uptake was decreased.[73] Although it has been shown that measuring myocardial glucose metabolism using PET with ^{18}F-2-deoxy-2-fluoro-D-glucose (^{18}FDG) tracers is feasible in patients with PAH,[74] inconsistent results have been reported. Some studies have shown that the ratio of RV glucose uptake to LV uptake is increased in PAH and is associated with disease severity.[75-77] However, it remains uncertain whether the increased ratio is due to increased RV glucose uptake[78-80] or decreased LV glucose uptake.[77] In addition, other studies have shown that the changes in the ratio of RV to LV glucose uptake did not correlate with

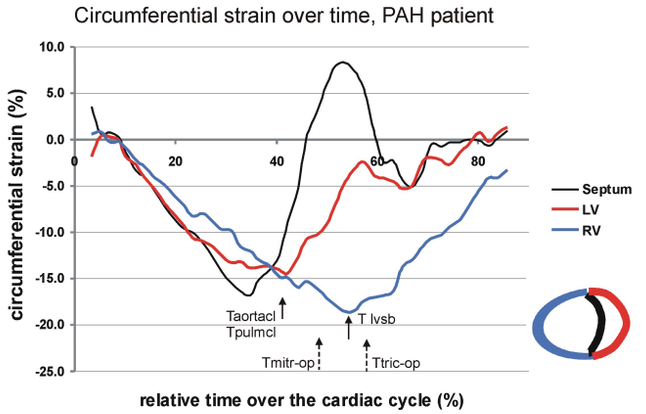

Figure 1. The presence of ventricular dyssynchrony illustrated in a patient with pulmonary arterial hypertension (PAH) measured by cardiac magnetic resonance imaging (CMR) strain analysis. Circumferential strain curves reflect myocardial shortening (negative strain) and stretching (positive stain) over time of the cardiac cycle for the right ventricular (RV) free wall (blue), left ventricular (LV) free wall (red), and interventricular septum (black). The LV, RV, and septum start simultaneously with shortening. However, RV peak shortening occurs later than LV peak shortening in the cardiac cycle. The aortic and pulmonary valves close ($T_{aortacl}$ and T_{pulmcl}) at the time of LV peak shortening. The time of maximal leftward septal bowing (T_{lvsb}) occurs coincidently with septal stretching and with peak shortening of the RV. $T_{mitr\text{-}op}$ and $T_{tric\text{-}op}$ indicate the opening times of the mitral and tricuspid valves and indicate the onset of LV and RV filling.

disease severity.[81] These conflicting results may be caused by differences in patient populations, scanning protocols, and data analysis. Other limitations could be that ^{18}FDG uptake is not a direct reflection of glycolysis, because ^{18}FDG uptake is also influenced by other factors, reflects the uptake of the overall myocardial tissue instead of the cellular uptake, and cannot appropriately be metabolized through all the glycolysis steps because of its chemical structure.[82] At this moment, clinical PET studies cannot provide firm answers about an eventual "metabolic switch" in the failing RV of patients with PAH, whereas this metabolic switch has been previously demonstrated in animal models.[83-85]

PERFUSION IMAGING AND OXYGEN BALANCE

Using PET with ^{11}C-acetate or a combination of $H_2{}^{15}O_-$, $^{15}O_{2-}$, $C^{15}O_-$ tracers, myocardial oxygen (O_2) consumption can be accurately measured. In PAH, it has been shown by PET imaging that the myocardial O_2 demand was increased, which was primarily determined by elevated pulmonary pressures and heart rate.[81,86] An increased myocardial O_2 demand can be balanced by 2 mechanisms, (1) coronary flow reserve and (2) myocardial O_2 extraction fraction (OEF) reserve. Although there are no normal human resting values of OEF, the resting value of OEF in dogs is 45%–50%.[87] This implies a significant OEF reserve in the normal RV and resembles the primary source for an augmented O_2 demand during exercise.[88] In patients with PAH, the resting OEF is significantly increased (~70%),[81] which infers that the OEF reserve in PAH is already limited at rest, and it has been suggested that the RV becomes more dependent on its coronary flow (like the LV).[89] However, despite a higher O_2 demand, RV myocardial blood flow remained unchanged. In addition, the elevated O_2 demand was related to impaired mechanical efficiency, which is a characteristic for a deteriorating RV (Fig. 2).[81] Similarly, it has been shown by CMR that right coronary blood flow is impaired in patients with PAH and was related to the amount of RV hypertrophy.[90] In addition, it has been demonstrated by PET that exercise-induced RV O_2 supply is limited.[91] In line with these findings, adenosine stress perfusion CMR in patients with PAH revealed that the perfusion reserve is restricted, not only in the RV, but also in the LV, which suggests that a systemic component plays a role in the development of RV dysfunction (Fig. 3).[92] These results imply that the increased RV O_2 demand in patients with PAH cannot be adequately balanced by an increase in O_2 supply. The possible consequences of ischemia have been illustrated by Gomez et al.,[93] who demonstrated by stress-induced SPECT RV wall ischemia at specific IVS insertion points that delayed contrast enhancement (DCE) was related to RV dysfunction. It has been repeatedly observed, using gadolinium contrast-enhanced CMR, that DCE appears as a unique pattern at the same IVS insertion points and is related to RV remodeling and dysfunction.[94-97] McCann et al.[96] showed that focal fibrosis could be the cause of DCE.

ANGIOGENIC IMAGING

Preclinical studies in PAH animal models have shown that RV ischemia and fibrosis may result from insufficient angiogenesis in the setting of rapid myocardial hypertrophy.[83,98] Perfusion and metabolic imaging provide indirect evaluation of angiogenic processes. Novel imaging strategies have been developed that can directly detect angiogenic molecular events. Vascular endothelial growth factor (VEGF) is the major contributor to angiogenesis, and adhesion molecules, such as integrins, are other important angiogenic modulators. In animal models of PH, capillary rarefaction and reduced VEGF expression have been demonstrated both in the RV and in the lungs.[98-101] Although not yet quantified in the lungs, PET imaging with ^{64}CU-

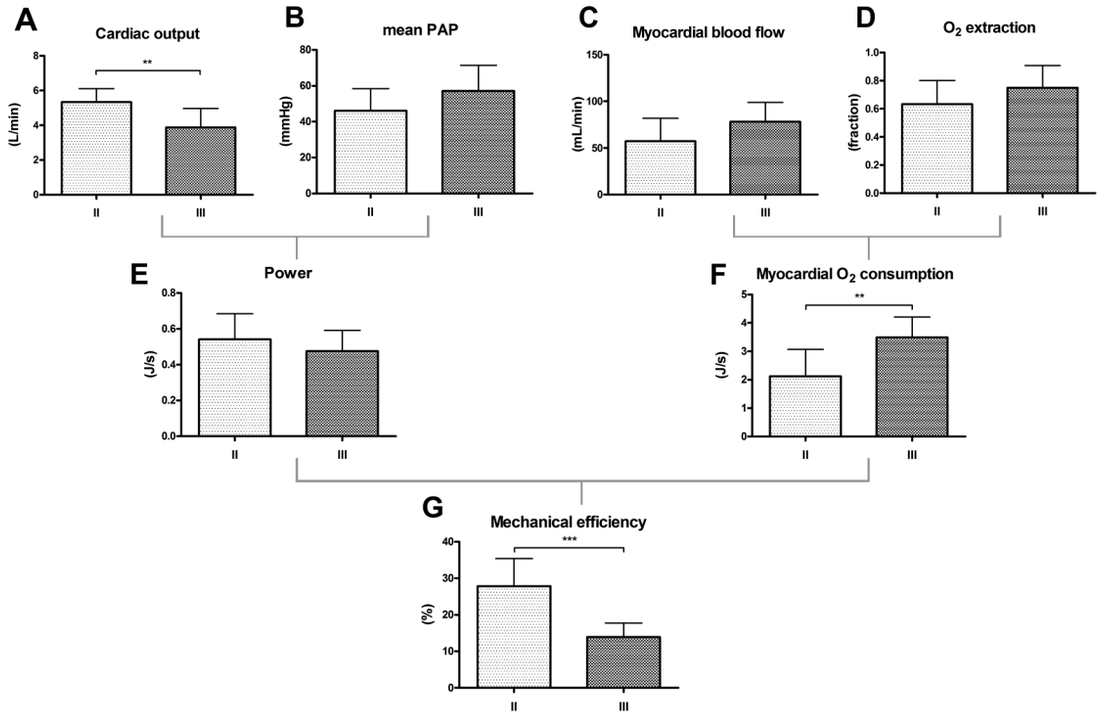

Figure 2. Impaired right ventricular (RV) mechanical efficiency in patients with idiopathic pulmonary arterial hypertension (IPAH) is primarily determined by increased myocardial oxygen consumption (MVO_2). Dark bars = New York Heart Association (NYHA) functional class III patients; light gray bars = NYHA functional class II patients. Cardiac output (CO) measured by cardiovascular magnetic resonance imaging (CMR) is higher in NYHA II patients than NYHA III patients (*A*), and mean pulmonary artery pressure (PAP) was similar in both groups (*B*). RV myocardial blood flow measured by positron emission tomography (PET) with $H_2{}^{15}O$ tracers (*C*) and oxygen (O_2) extraction fraction estimated by PET using $^{15}O_2$ tracers (*D*) were not statistically higher in NYHA III patients compared with NYHA II patients. RV power output (i.e., product of CO and mean PAP) was comparable in both groups (*E*). There was a significantly higher MVO_2 per gram of myocardial tissue in NYHA III patients compared with NYHA II patients (*F*). A similar RV power output but higher MVO_2 led to a significant reduction in RV mechanical efficiency (i.e., ratio of RV power output and MVO_2) of ~50% in NYHA III patients compared with NYHA II patients (*G*). Reprinted with permission from Wong et al.[81]

labeled $VEGF_{121}$ or ^{18}F arginine-glycine-aspartic acid peptide (RGD) with affinity for the $\alpha_v\beta_3$ integrins have enabled measurements of angiogenic myocardial repair processes in rat models with myocardial infarction.[102-104] Other tissue processes, such as apoptosis, can be localized and quantified using in vivo CMR annexin imaging.[105] These imaging techniques might be important to study pathophysiological pathways of myocardial disease processes in vivo and can provide longitudinal monitoring to detect therapeutic responses.

HYBRID IMAGING

Hybrid imaging provides optimal in vivo evaluation of RV hemodynamic consequences by integration of anatomical information with physiological and molecular imaging in the same setting. It allows molecular imaging per anatomic region or per gram of myocardial tissue. PET/CT has become commonplace in clinical practice and research settings and has significantly contributed to our insights in pathophysiological processes in cardiovascular disease.[106] Hybrid PET/magnetic resonance imaging (MRI) is an innovative, fast-upcoming technique and not only allows simultaneous combination of PET with anatomic imaging but also provides functional imaging, perfusion, tissue characterization, and flow imaging, thereby improving clinical application and stratification of patients with RV failure. Figure 4 demonstrates CT/PET ^{18}F-Galakto-RGD imaging of integrin expression in a patient 2 weeks after myocardial infarction.[107] Although measured sequentially, CMR delayed enhancement showed the exact anatomical localization of tracer retention in the infarcted area. In addition, the first case reports and small patient series using cardiac hybrid PET/MRI imaging have been published.[108-110] However, one limitation of hybrid systems with MRI is that it does not provide information required for attenuation correction of nuclear images. Although it remains particularly

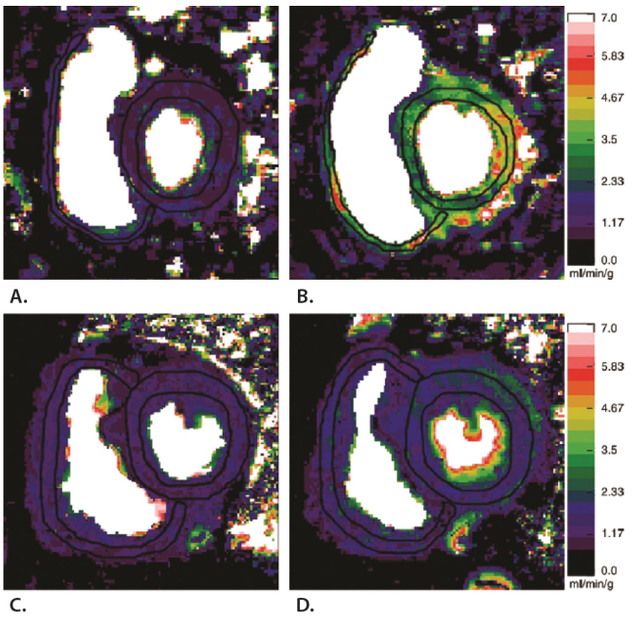

Figure 3. Representative perfusion maps showing that biventricular perfusion reserve was diminished in patients with pulmonary arterial hypertension (PAH) compared with controls. Cardiovascular magnetic resonance imaging perfusion maps of the right ventricle (RV) and left ventricle (LV) were obtained under resting conditions and after adenosine induced stress. Perfusion scales are on the right. Myocardial perfusion at rest in a healthy control subject (*A*) is significantly increased during adenosine stress (*B*). *C*, Resting myocardial perfusion in the hypertrophic RV of a patient with PAH. *D*, After adenosine stress, myocardial perfusion does not increase in both the LV and RV, illustrating that the perfusion reserve is limited in patients with PAH compared with controls. Reprinted with permission from Vogel-Claussen et al.[92]

challenging to measure density variations in the lungs, this has become an active area of research.[111,112]

IMAGING IN CLINICAL PRACTICE

RV imaging parameters might provide important information for the diagnosis and risk stratification of patients with PAH and could also be helpful in therapeutic decision making. Current PAH targeted medical therapies (i.e., prostacyclins, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors) can affect the RV directly or indirectly through lowering of load. Although CT is considered part of the diagnostic work-up of patients with PH, the clinical relevance of RV assessment by CT has not been demonstrated.[113] Echocardiography is readily available in clinical practice and can be helpful in the detection of the cause of PH. Measures of pericardial effusion and TAPSE are considered of prognostic relevance and as treatment parameters during follow-up.[113,114] Although serial assessment of echocardiographic RV longitudinal strain and strain rate could provide therapeutic information,[115,116] the clinical role of these newer echocardiographic modali-

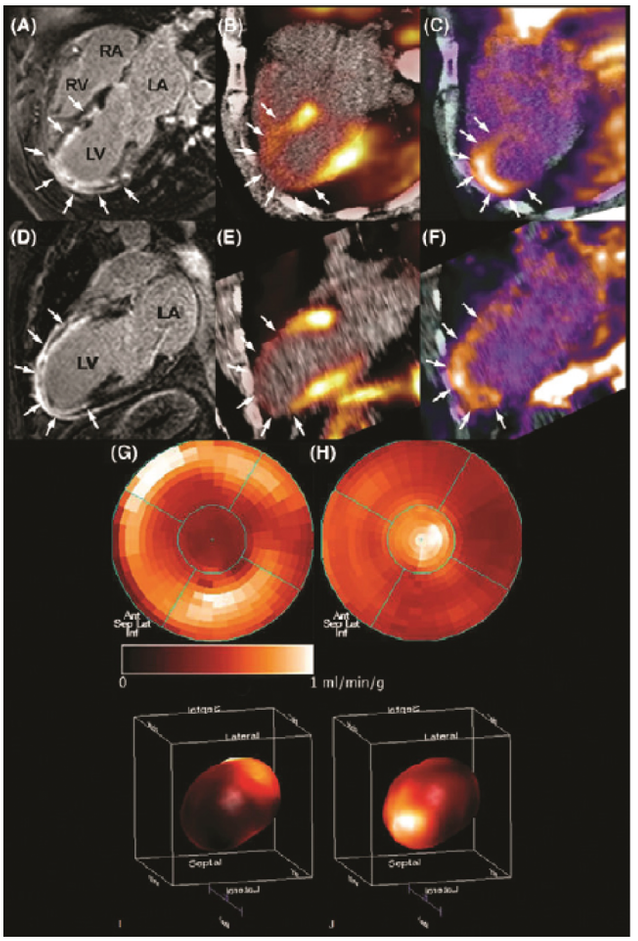

Figure 4. In vivo molecular imaging of angiogenesis in a patient after acute myocardial infarction. Two weeks after acute myocardial infarction and percutaneous coronary intervention, a patient underwent cardiovascular magnetic resonance imaging (CMR) and positron emission tomography (PET)/computed tomography (CT). CMR gadolinium delayed contrast enhancement (DCE) was observed almost transmural in the anterior, anteriorseptal, anteriorlateral, and apical left ventricle wall (*A, D*). PET imaging with ^{13}N-ammonia revealed impaired myocardial blood flow in correspondence with the regions of DCE (*arrows; B, E*). PET with the agent ^{18}F arginine-glycine-aspartic acid peptide (^{18}F-RGD), with affinity for the $\alpha_v\beta_3$ integrins, demonstrated focal signal areas in the infarcted area (*C, F*). This signal may reflect angiogenesis within the healing area (*arrows*). Polar maps of myocardial blood flow assessed by PET with ^{13}N-ammonia (*G, I*) show severely reduced blood flow in the distal left anterior descending coronary artery perfusion region. Co-localized ^{18}F-RGD signal corresponded to the regions of reduced blood flow (*H, J*), demonstrating the extent of the $\alpha_v\beta_3$ integrin expression in the infarcted area. Reprinted with permission from Makowski et al.[107]

ties has to be determined. At present, the clinical value of CMR has been clearly established,[12] and clinical decision making increasingly relies on measurements of RV volumes and function and their trends during follow-up. It has been suggested that considering RV imaging parameters as end points in clinical trials could be of clinical importance,[117] but only a few studies have evaluated cardiac parameters as therapeutic outcomes, and most studies included small patient populations. Recently, the EURO-MR study has shown that changes in global RV function measures after medical treatment reflect changes in functional class and survival in patients with PAH.[118] RV mass has been shown to be a valuable end point in clinical trials, but a clinically relevant change has not been determined.[119,120] Stroke volume obtained by CMR is the only imaging parameter that has been validated to monitor therapeutic effects, and a clinically relevant change was found to be greater than 10 mL.[26] The role of PET imaging in PH has been primarily restricted to investigational imaging, and its clinical applicability is currently limited. However, PET techniques allow assessment of pathophysiological pathways of myocardial disease processes in vivo and therefore have great potential to monitor therapeutic responses longitudinally in the near future. One study has demonstrated that PET RV ^{18}FDG uptake might be of clinical relevance after epoprostenol therapy.[80] Future studies are required to validate RV imaging parameters to assess therapeutic effects.

SUMMARY

The RV determines symptoms and survival in patients with PAH. Therefore, insights in the pathophysiology of RV failure and the identification of risk factors, prognostic factors, and indicators to measure treatment response on a regular basis associated with the RV are required, and it is preferred that these be determined noninvasively. Advanced imaging techniques have evolved that provide noninvasive, in vivo information about the RV in the setting of chronic pressure overload. These techniques provide complementary RV information: CT provides morphological imaging, CMR provides global volumetric and functional analyses, echocardiography provides the assessment of regional RV function, and PET provides perfusion and molecular imaging. Therefore, integrated application of these techniques could provide full insights into the different pathophysiological aspects of a failing RV in patients with PAH. Recent developments in hybrid imaging will implement simultaneous measurements of myocardial and vascular interactions and will be one of the most important potential future developments.

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