CARDIAC PET, CT, AND MRI (P SCHOENHAGEN AND P-H CHEN, SECTION EDITORS)



Multimodality Imaging for Cardiac Evaluation in Patients with COVID-19

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Accepted: 17 February 2021 / Published online: 15 March 2021 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC part of Springer Nature 2021

Abstract

Purpose of Review A growing number of cardiovascular manifestations resulting from the novel SARS-CoV-2 coronavirus (COVID-19) have been described since the beginning of this global pandemic. Acute myocardial injury is common in this population and is associated with higher rates of morbidity and mortality. The focus of this review centers on the recent applications of multimodality imaging in the diagnosis and management of COVID-19-related cardiovascular conditions.

Recent Findings In addition to standard cardiac imaging techniques such as transthoracic echocardiography, other modalities including computed tomography and cardiac magnetic resonance imaging have emerged as useful adjuncts in select patients with COVID-19 infection, particularly those with suspected ischemic and nonischemic myocardial injury. Data have also emerged suggesting lasting COVID-19 subclinical cardiac effects, which may have long-term prognostic implications.

Summary With the spectrum of COVID-19 cardiovascular manifestations observed thus far, it is important for clinicians to recognize the role, strengths, and limitations of multimodality imaging techniques in this patient population.

Keywords COVID-19 · Cardiovascular · Myocardial injury · Multimodality imaging

Introduction

Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in high rates of worldwide morbidity and mortality. While the most common organ system affected remains the respiratory tract, a wide variety of important cardiac manifestations have been described [1, 2]. Acute

This article is part of the Topical Collection on Cardiac PET, CT, and MRI

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Nisha A. Gilotra naggarw@jhmi.edu myocardial injury, defined by elevated troponin level above the 99th percentile upper reference limit, is relatively common in COVID-19 and is independently associated with adverse outcomes [3, 4]. Furthermore, patients with COVID-19 are at risk for cardiovascular (CV) events including cardiac arrhythmias, myocardial infarction, heart failure, and stroke [1]. With increasing recognition of CV complications of COVID-19, the role of cardiac imaging techniques used to diagnose,

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manage, and monitor COVID-19 patients has evolved [5•, 6•]. More recent studies have focused on the detection of subclinical cardiac dysfunction and persistent cardiac inflammation and scar resulting from myocardial injury.

Pathophysiology of COVID-19 Cardiovascular Effects

The reported incidence of myocardial injury, as measured by troponin, has been widely variable, ranging from 7 to 51% in COVID-19 patient cohorts [7, $8 \cdot$, 9]. The forms of COVID-19-related CV injury generally fall into the following categories: primary damage resulting from direct viral effect; secondary damage as a consequence of other organ or systemic dysfunction; and importantly, exacerbation of baseline CV disease by either primary or secondary causes [10]. The reported CV complications have included clinical and subclinical myocardial dysfunction, heart failure, myocarditis, cardiac arrhythmias, myocardial infarction, stress cardiomyopathy, pericarditis, vasculitis, circulatory shock, pulmonary hypertension, and thromboembolism [2, 11–13].

Although there is a wide range of documented effects on the CV system in COVID-19, the underlying cellular mechanisms are multifaceted and incompletely understood [12, 14-16]. SARS-CoV-2 gains entry into cells via binding of its viral spike protein to angiotensin-converting enzyme 2 (ACE2), which resides on a variety of cell surfaces throughout the body, including cardiomyocytes and vascular endothelial cells [17, 18]. A common initial point of entry is the respiratory epithelial cell, which has high levels of ACE2 [19]. Subsequent viral invasion of other tissues expressing membrane-bound ACE2, such as the myocardium, can then occur with resultant cytotoxicity and organ dysfunction. Autopsy studies have demonstrated evidence of viremia with SARS-CoV-2 RNA and active replication particles in myocardial interstitial tissue [20, 21]. Direct viral invasion of vascular endothelial cells with associated inflammation and damage to the vascular endothelial membrane has also been discovered on histological specimens [22].

A major consequence of SARS-CoV-2 viral replication and hematogenous spread is the downregulation of ACE2, resulting in numerous adverse downstream effects. Loss of ACE2 reduces degradation of angiotensin II, thus leading to cardiomyocyte hypertrophy, myocardial and endothelial dysfunction, vasoconstriction, and local inflammation [23, 24]. Similar processes additionally lead to platelet dysfunction and heightened thrombosis [25, 26]. Furthermore, indirect cellular damage is hypothesized to occur by widespread immune activation and cytokine release [11, 25, 27–29]. Significant elevations in proinflammatory cytokines such as interleukin-6, C-reactive protein, tumor necrosis factor alpha, and ferritin in patients with COVID-19 are frequently reported [30–32]. These circulating molecules may then release reactive oxygen species, acutely depress myocardial contractility, trigger cardiac arrhythmias, cause localized arterial inflammation, and lead to secondary CV damage via cardiomyopathy, acute coronary syndrome, and thrombosis [11, 25, 27]. Other secondary mechanisms of injury include electrolyte imbalance, hypoxia, medication effect, catecholamine surge, and overall increased cardiometabolic demand [25]. Given the breadth of potential cardiovascular effects of COVID-19, multimodality imaging can provide integral information to guide diagnosis and management.

Cardiac Imaging Modalities in COVID-19

Echocardiography

The most commonly utilized imaging modality for dedicated cardiac evaluation in COVID-19 is transthoracic echocardiography (TTE), which is safe, easily accessible, and portable. Although many have reported a high incidence of myocardial injury based on troponin elevation in COVID-19, Giustino et al. found that myocardial injury plus abnormal finding on TTE, but not myocardial injury alone, were associated with a higher risk of death, suggesting an added prognostic benefit to this imaging modality [33]. When compared to acute respiratory distress (ARDS) patients without COVID-19, those with COVID-19-related ARDS have similar troponin levels, which can be largely explained by underlying comorbidities and illness severity [8•]. This may suggest incremental value in cardiac imaging beyond a serum troponin level. The major benefits to TTE are the ability to be rapidly performed at the patient's bedside, relative ease of use, and lack of radiation (Table 1). The American Society of Echocardiography has issued statements to guide clinicians on use of TTE safely, efficiently, and appropriately amidst the COVID-19 pandemic [34••, 35]. One of the drawbacks of TTE, and the major reason use has been discouraged in COVID-19 patients who are lacking a specific cardiopulmonary question to be answered, is the viral transmission risk. TTE requires sonographers to make direct and prolonged patient contact [36]. Despite these risks, TTE is considered by major society guidelines to be a safe option when there is an appropriate clinical indication and when sanitization and PPE guidelines are followed [34.., 37].

Standard TTE ultrasound images can provide important information about cardiac structure and function. In an international prospective survey of 1216 COVID-19 patients undergoing TTE, the most common imaging indications were suspected heart failure in 40%, cardiac biomarker elevation in 26%, and right-sided heart failure in 20%, which changed patient management in 33% of cases [38]. Both left and right ventricular functional assessments are essential in patients with suspected cardiomyopathy, myocarditis, myocardial infarction,

pulmonary hypertension, or pulmonary embolism. Abnormal left ventricular (LV) systolic function is primarily detected as reduced LV ejection fraction (LVEF) and/or focal LV wall motion abnormalities on TTE. A specific pattern of predominantly apical LV wall motion abnormality with or without apical ballooning can support a diagnosis of stress-induced, or Takotsubo, cardiomyopathy [39]. This condition can occur more often in patients with sepsis, shock, or hypoxia, and despite typically being a diagnosis of exclusion, has been described in several reports of COVID-19 patients [40, 41]. Due to frequent difficulties in adequate image acquisition in the critically ill COVID-19 patients, it is important to note that the use of ultrasonic enhancing agents (commonly known as echocardiographic contrast) can safely improve the diagnostic yield of bedside TTE [42]. The aforementioned international

study by Dweck et al. reported LV abnormalities in 39% of patients, and LVEF was <50% in over 25% of patients in a similar cohort [33, 43]. However, this moderate prevalence of LV systolic dysfunction is not consistent across all studies investigating echocardiography in COVID-19. Another study reported that among 100 COVID-19 patients who underwent TTE within 24 h of admission, the most common findings were right ventricular (RV) dilation and dysfunction in 39% and LV systolic dysfunction in only 10% [44].

RV function is commonly assessed by quantifying chamber size, tricuspid annular plane systolic excursion (TAPSE), and RV systolic velocity via tissue Doppler imaging [45]. Isolated RV dysfunction in the setting of COVID-19 infection may suggest acute pulmonary hypertension, right-sided myocardial infarction, or even focal myocarditis [46]. Given the high

Table 1	Characteristics	of imaging	modalities for	COVID-19	patient care
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Imaging modality	Advantages	Disadvantages	COVID-19 findings
Echocardiography	Rapid Performed bedside	Sonographer infectious exposure	• RV dilation and dysfunction
	No radiation	• Image quality often compromised by patient habitus or ventilation	• LV systolic and diastolic dysfunction
	• Low cost		Wall motion abnormalities
			Stress cardiomyopathy
			Pulmonary hypertension
			Reduced LV and RV strain
			Pericardial effusion
			• Elevated filling pressures
Point-of-care ultrasound	• Rapid • Performed bedside	• Infectious exposure to provider	Basic LV and RV structural and functional abnormalities
	No radiation		
	 Low cost Minimal equipment	• Image quality compromised by patient	Pericardial effusion
		habitus or ventilation	Pleural effusion
		• More limited functionality compared to echocardiography	• B lines (may indicate interstitial edema on lung ultrasound)
CT/CTPA/CTA	• Rapid	Radiation	Pulmonary embolism
	High resolution	Risks of iodine contrast	Cardiomegaly
			Chamber size
	Moderate cost	• Not bedside	Intracardiac thrombus
	Some tissue characterization		Pericardial effusion
CMR	High resolution	• Expensive	• Ischemic vs nonischemic injury
	 Functional imaging 	Time-consuming	Stress cardiomyopathy
	Superior tissue characterization	• Frequent patient intolerance and incompatibilities	Myocarditis
			Pericarditis
	No radiation		Chamber enlargement
			Strain abnormalities
Nuclear imaging	Inflammation localization	Low resolutionTime-consuming	• Valvular inflammation in endocarditis (FDG-PET alternative to TEE)
		Radiation exposure	Myocardial inflammation in myocarditis

incidence of ARDS requiring mechanical ventilation and the hypercoagulable state of many patients with severe COVID-19, it is thought that damage to both the lung parenchyma and the pulmonary microvasculature contributes to RV dilation and dysfunction in this setting [47]. Cor pulmonale due to a sudden increase in RV afterload has also been reported [48]. In COVID-19, this most commonly results from pulmonary embolism or hypoxic respiratory failure with elevated airway pressures. Nonetheless, the finding of RV dysfunction or remodeling portends a poor overall prognosis in COVID-19 [46, 49, 50]. In addition, positive end-expiratory pressure, a common adjunctive support in COVID-19 lung disease, can acutely impair the RV, and such dysfunction that persists on repeat TTE has been shown to correlate with adverse outcomes [51].

LV diastolic dysfunction is most commonly assessed with pulse wave Doppler at the level of the mitral valve in combination with chamber sizes and may be the only TTE abnormality seen in patients with heart failure with preserved ejection fraction [52]. Diastolic dysfunction has been reported in COVID-19, though it can be difficult to determine the acuity of this finding in patients with high prevalence of underlying comorbidities such as hypertension and diabetes [44]. The mitral valve E/e' ratio can be used to noninvasively estimate left-sided cardiac filling pressure, and has been shown to be elevated frequently in patients with COVID-19 [52, 53].

As can also be seen on standard TTE, pericardial effusions have been noted in several COVID-19 case studies, along with the rare yet important diagnosis of pericardial tamponade secondary to COVID-19 pericarditis or perimyocarditis [54–58]. These effusions are likely related to active inflammation in the setting of systemic infection.

Specialized Echocardiographic Techniques

In the era of COVID-19, point-of-care ultrasound (POCUS) has emerged as an adjunct to standard TTE and has played an important role in the care of COVID-19 patients by allowing for more rapid patient assessment with lower equipment burden and viral transmission risk [59]. POCUS can generally be used to quickly assess the same transthoracic structures discussed above, albeit at slightly lower resolution and often without Doppler features [60, 61]. Abnormal findings on POCUS have been utilized to identify patients who might benefit from complete TTE and thus limit unnecessary testing and exposures. It has also been used to monitor certain cardiac or pulmonary parameters over time when serial TTE, or clinical physical exam, were not easily obtained [60]. POCUS has been highly utilized for bedside lung ultrasound during the COVID-19 pandemic, showing strong ability to identify small pleural effusions and parenchymal consolidations and thus limiting the need for chest computed tomography (CT) in many cases [62].

Recent technological advances have expanded the diagnostic and prognostic capabilities of standard echocardiography. Speckle tracking echocardiography (STE) is a newer noninvasive modality used in conjunction with conventional 2dimensional-based TTE that calculates the percent change in myocardial deformation throughout the cardiac cycle to provide precise estimation of regional and global contractile function known as strain [63]. Although most commonly used for the LV, STE can be applied to any chamber utilizing an offline post-processing software and has proven useful in identifying subclinical myocardial dysfunction in COVID-19 [64]. Both LV and RV strain have been found to be significantly reduced and predictive of mortality in patients with COVID-19 (Fig. 1) [50, 64, 65]. A frequent pattern of basal LV strain reduction has also been reported, suggesting areas of enhanced myocardial susceptibility to COVID-19-related damage [66, 67]. One study determined that longitudinal assessment of RV function via TAPSE and RV free-wall strain actually underestimated the degree of radial impairment in COVID-19 and suggested that RV fractional area change (FAC) and RV-pulmonary artery coupling (calculated as FAC/RVSP) may be more useful measurements of RV function in COVID-19 [68].

A newer advance in echocardiography is myocardial work assessment, which uses STE-derived strain indexed to systolic blood pressure to provide a more load-independent measure of systolic function. It has not been extensively studied in COVID-19; however, reduced myocardial work efficiency has been associated with increased mortality, and one case report noted reduced myocardial work index as the only abnormal, and thus possibly an early, marker of myocardial dysfunction using TTE [69, 70].

Transesophageal Echocardiography

Due to heightened infectious risk from patient aerosol production, the use of transesophageal echocardiography (TEE) has declined since the outbreak of COVID-19 in favor of noninvasive imaging options, when available. The American Society of Echocardiography released guidelines specifically instructing providers to defer TEE whenever feasible in patients with COVID positivity [34••]. As a result, many institutions have transitioned from the utilization of TEE for some indications such as exclusion of left atrial appendage thrombus prior to cardioversion to gated cardiac CT when feasible [71].

Computed Tomography

The role of CT in COVID-19 patient care began early in the pandemic, as many patients undergo chest CT in the diagnostic workup for respiratory symptoms. Benefits to this modality include quick speed, high spatial resolution and tissue characterization, and noninvasive nature, while the cons consist of radiation exposure and the risks of administering intravenous contrast (Table 1) [72]. The discussion of CT utility in the COVID-19 literature to date mainly focuses on the evaluation



Fig. 1 Examples of imaging findings in COVID-19. (a) Computed tomography-pulmonary angiography (CTPA) displaying a saddle pulmonary embolism (blue arrow). (b) Transthoracic echocardiography images showing reduced global left ventricular (LV) strain at -12.6%.

Cardiac magnetic resonance scan showing (c) patchy late gadolinium enhancement of the LV consistent with scar/fibrosis with (d) prominent mid-myocardial enhancement (red arrow) seen in the short-axis view

for pulmonary embolism, myocarditis, acute coronary syndrome, and exclusion of left atrial thrombi prior to cardioversion; however, there is value in the evaluation of other CV complications as well [72, 73].

When performed as a non-contrast, non-cardiac-gated scan, CT insights into cardiac structure and function are largely limited to morphology of heart chambers and great vessels and presence of pericardial effusion. In addition, CT enables the quantification of coronary calcifications which are not inherently related to COVID-19 infection, however, are common in patients with CV risk factors, and frequently present in hospitalized COVID-19 patients [74]. CT of the chest without contrast mainly ordered for evaluation of lung pathology in COVID-19 can also provide important CV information, especially in the setting of acute or chronic kidney injury precluding the use of intravenous contrast. For example, imaging features of heart failure such as the appearance of pulmonary veins can be detected with chest CT, and this modality has been shown to be helpful in differentiating COVID-19 pneumonia from acute decompensated heart failure when presenting signs and symptoms were similar and difficult to distinguish clinically [75].

When contrast is used with chest CT, however, as in the case of the CT-pulmonary angiography (CTPA) for pulmonary embolism evaluation, it provides more detailed information relevant to CV complications (Fig. 1). COVID-19 infection leads to a hypercoagulable state, and studies have cited high rates of pulmonary embolism incidence, ranging from 2.6 to 24% [76-78]. Accordingly, CTPA can also diagnose right atrial thrombus, which has been seen in COVID-19 patients [79]. In addition to diagnosing the presence and grading the severity of pulmonary emboli, CTPA allows for better visualization of cardiac chamber size, intraventricular septal bowing, and aortic pathology. Contrast-enhanced CT can be combined with cardiac gating to evaluate for myocardial edema, scarring, and fibrosis when cardiac magnetic resonance imaging (CMR) is unavailable. Cardiac CT in these cases can be useful in the evaluation of COVID-19 myocarditis via subepicardial delayed enhancement [71, 80]. Specifically, when a patient presents with new LV dysfunction and echocardiographic wall motion abnormalities that are not in a typical coronary distribution, further focused testing should be employed to evaluate for myocarditis, myocardial infarction with nonobstructive coronary arteries (MINOCA), and other

forms of cardiomyopathy [5]. Although not commonly used in clinical practice yet for the evaluation of myocardial fibrosis, cardiac CT has proven capable of detecting myocardial scar and assessing extracellular volume using late iodine contrast enhancement [81].

As previously noted, cardiac CT angiography (CTA) may be an acceptable alternative to TEE for the exclusion of left atrial appendage thrombus, when feasible [71, 73]. Similarly, multiphase cardiac CT has also been used for evaluation of endocarditis and paravalvular complications instead of TEE [71]. Coronary CTA has gained greater utility as a method to evaluate for coronary artery disease, for example, in the case of elevated troponin levels of unclear etiology, sometimes avoiding the need for invasive coronary angiography [71]. Limitations in elective stress testing due to the pandemic have also contributed to the increase in use of coronary CTA.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging has rapidly emerged to become an important imaging modality used in the assessment of COVID-19-related myocardial injury. Due to its high resolution morphological and functional imaging capabilities, as well as tissue characterization, CMR is often used to aid in diagnosis of cardiomyopathies [82]. Some common barriers to widespread use of CMR use include metal incompatibilities, long scanning durations, gadolinium risks, patient claustrophobia, and high expense compared to other modalities (Table 1). More specific to the COVID-19 patient population, CMR can require a larger amount of disinfection time between scans, and patient variables such as stability, ventilation status, position, and ability to breath-hold can prevent acquisition of certain images [83]. However, society guidelines have provided practitioners with guidance on the safe CMR scanning of COVID-19 patients [84].

One of the primary advantages of CMR is the ability to help differentiate between ischemic and nonischemic myocardial injury. Although the gold standard for the diagnosis of myocarditis requires myocardial biopsy, the Lake Louise Consensus Criteria have provided proposed diagnostic criteria for myocarditis using standard CMR and later updated to include the use of parametric mapping techniques [82, 85]. Myocardial edema with late gadolinium enhancement (LGE) in a non-coronary distribution along with CMR tissue characterization (T1 and T2 mapping) showing increased T1 and T2, indicative of cardiac edema, inflammation, and fibrosis, may be seen in myocarditis. The largest study to date evaluating the utility of CMR in COVID-19 patients is a systematic review of 34 studies including 199 patients [86]. The study found that the most common diagnosis made by CMR in this population was myocarditis (40%) with significant T1 and T2 mapping abnormalities, T2/short-T1 inversion recovery (STIR) edema, and LGE [86]. Other notable diagnoses that can be made with CMR include pericarditis, MINOCA, and stress cardiomyopathy [87].

CMR has gained additional recognition and utility in patients clinically recovered from COVID-19. Puntmann et al. reported that 78% of recently recovered COVID-19 patients had an abnormality on CMR, and 60% had findings consistent with ongoing myocardial inflammation [88]. These findings raise concern for long-term CV complications secondary to COVID-19, even in asymptomatic patients. Similarly, studies of CMR performed after asymptomatic or mildly symptomatic COVID-19 infection in college-aged athletes found evidence of active myocardial inflammation in 15% and prior myocardial injury in 31% [89]. However, when compared to an athletic control group, 3% of recovered COVID-19-positive athletes had findings of myocarditis, with the only significant difference being increased midseptal edema in the COVID-19 group [90]. Further studies are needed to determine the optimal screening modality for long-term cardiac sequelae. Other forms of myocarditis showing LGE on CMR have correlated with malignant arrhythmias and sudden cardiac death in the convalescent phase of infection, and may serve as an important consideration in the management of COVID-19 survivors [91, 92]. CMR might additionally be a useful modality in making exercise recommendations post-COVID-19 in a select population, and publications discussing the issue of sports resumption after COVID-19 infection have emerged [93, 94].

Nuclear Imaging Techniques

Similar to other modalities, postponement of all non-urgent nuclear cardiology studies has been encouraged, and societal safety principles have been published [95, 96••]. When appropriate, pharmacologic rather than exercise stress testing has been encouraged to limit aerosol generation. Fluorodeoxyglucose (FDG) positron-emission tomography (PET) has been used as an alternative to TEE in the evaluation of suspected endocarditis during the pandemic [95]. In general, however, due to the inherent limitations in nuclear imaging studies, there has not been a specific clinical utility in this modality for COVID-19 patient evaluation [72]. FDG-PET imaging is currently used clinically in diagnosis and risk assessment of other forms of myocarditis, most notably cardiac sarcoidosis [97]. This utility may add incremental value to the evaluation of COVID-19 myocarditis.

Safety Precautions

Regardless of the imaging modality used for patient care in the COVID-19 era, the safety of patients and healthcare providers remains a universal priority. The importance of proper PPE and limiting of testing to that which impacts patient health and

Fig. 2 Flow chart illustrating the potential role of cardiovascular imaging in hospitalized patients with acute COVID-19 and suspected cardiac disease (a), and the role of imaging in the chronic care of recovered COVID-19 patients in the clinic setting (b)



clinical management has been emphasized in COVID-19 recommendations [34, 84, 98]. Additional considerations include anticipating delays secondary to symptom screening, sanitizing practices, and case backlogs [96••]. Choosing one best test for a patient can mitigate many infectious and logistical concerns. Therefore, it is beneficial for clinicians to know the strengths and limitations of available imaging modalities (Table 1).

Conclusions

As the pathophysiology and extent of possible CV involvement by COVID-19 is further recognized, the role of imaging in diagnosis, management, and prognosis of this disease will continue to evolve. Current society statements and guidelines recommend limiting imaging to that which is emergent or projected to change patient management [34, 36, 98, 99]. Tests that may answer clinical questions with less viral transmission risk are additionally preferable, when possible. In this light, echocardiography has become a primary tool for most COVID-19 patients with evidence of myocardial injury. CTA has become more heavily utilized for patients with suspected ischemic injury or thrombosis. For those with myocardial injury from nonischemic or unclear causes, CMR has taken on an important role. Early data suggests that CV consequences of COVID-19 can result in lasting subclinical myocardial inflammation or fibrosis detected on imaging. However, there are currently no standard guidelines on the optimal use of CV imaging in COVID-19 survivors with ongoing symptoms that may be cardiac, although the proposed clinical role of imaging in the acute and chronic setting (Fig. 2a and 2b) is reasonable considering the current evidence. It is likely that the role of CV imaging in post-COVID-19 care will continue to expand with ongoing investigation of this novel disease.

Funding Dr Goerlich is supported by the Ruth L. Kirschstein Institutional National Research Service Award T32HL007227-Pathophysiology of Myocardial Disease. Dr Minhas is supported by the National Heart, Lung, and Blood Institute training grant T32HL007024. Dr Mukherjee is supported by the Johns Hopkins Clinician Scientist Award, Johns Hopkins Magic That Matters Fund, NIH/NHLBI (R01 01HL114910), and the Department of Defense (W81XWH2010768). Dr Hays is supported by the Magic that Matters Fund of Johns Hopkins Medicine and National Institutes of Health/National Heart Lung and Blood Institute 1R01HL147660.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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