 doi:10.20944/preprints202205.0030.v1

Review

Pulmonary Hypertension and the Development of Right Ventricular Hypertrophy among COVID-19 Patients

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Abstract: COVID-19 affects many organs in our body, including the heart and lungs. COVID-19 cases that require hospitalization often exhibit pulmonary hypertension (PH) due to changes in the lung microvasculature in which the blood vessels become stiff, damaged, or narrow, causing increased pulmonary arterial pressure. This review examines the hypothesis that PH can lead to right ventricular hypertrophy (RVH) as a long-lasting aftereffect of COVID-19. Recent studies have shown that significant percentages of hospitalized patients develop right ventricular hypertension and right ventricular dilatation (RVD), which may lead to right ventricular failure and death. Despite recommendations for echocardiogram reports to include right ventricular wall thickness to assess RVH, few published reports have reported this parameter. Relevant studies on animal models of PH in which the timing of PH can be precisely controlled suggest that one to three weeks of PH can cause RVH. Thus, according to the hypothesis proposed here COVID-19 patients who have long-lasting severe disease (e.g., needed to be on a ventilator for one or more weeks) accompanied by PH and RVD may develop RVH as a long-lasting sequela outlasting the infection itself. Echocardiogram studies of recovered COVID-19 patients may determine whether oft-reported cardiovascular sequelae include RVH.

Keywords: animal models; cardiac aftereffects; COVID-19; hypoxia; echocardiogram; pulmonary hypertension; right ventricular dilatation; right ventricular hypertrophy

1. Introduction

COVID-19 is a rapidly developing disease that affects many organ systems, especially the cardiovascular and pulmonary systems. In fact, several studies have shown that patients with COVID-19 develop cardiac injury [1-4]. Shi et al. [2] noted that 19.7% of their study's participants developed cardiac injury during hospitalization and notes that cardiac injury is an "independent risk factor for in-hospital mortality." Another study has determined that a COVID-19-associated cytokine storm can lead to excessive neutrophil recruitment which is then responsible for organ damage and result in myocardial infarction [5].

COVID-19 cases that require hospitalization also often exhibit pulmonary hypertension (PH) [6]. PH develops when blood vessels in the lungs become stiff, damaged, or narrow, which causes the blood pressure in the arteries of the lungs to be abnormally high and makes the right side of the heart work harder to pump blood to the lungs [7]. Ultimately, PH can cause the heart to lose ability to pump enough blood through the lungs. PH can occur at all ages, but incidence typically increases with age. PH is more common among women, non-Hispanic blacks, and people aged 65 or older and is commonly found with heart failure [8]. PH can be either idiopathic or can be caused by other injuries and diseases [9]. PH during COVID-19 might be one of the causal factors of cardiac dysfunction that occurs during the disease.

A frequent result of PH is the development of cardiac dysfunction, particularly of the right ventricle which pumps blood to the lungs. Right ventricular dysfunction caused by PH encompasses right ventricular dilatation (VHD), right ventricular hyper-

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trophy (RVH), and heart failure (HF). The potential for PH to cause right ventricular dysfunction has been observed for many conditions. For example, hemodialysis patients have been noted to exhibit PH and associated RVD and RVH, with a significant increase in right ventricular wall thickening [10]. Similarly, high serum phenylalanine has been associated with PH and cardiac dysfunction in newborns and in a rat model, injections of phenylalanine caused PH and significant associated RVH within two weeks [11]. So, it is important to know if RVH similarly occurs as a result of COVID-19 associated PH.

2. Hypothesis

We hypothesize that patients who have long-lasting severe COVID-19 (e.g. needed to be on a ventilator for one or more weeks) accompanied by PH will develop RVH. This hypertrophy may be a long-lasting aftereffect resulting from COVID-19 disease.

3. Literature analysis

3.1. Heart Structure Changes in Patients with COVID-19

Numerous examples are now found in the literature of COVID-19 patients that develop PH and having accompanying changes in their right ventricle. An exemplar case study is reported by van Dongen et al. [12] who cared for a patient who had COVID-19 pneumonia, was on a ventilator for "a few days" and after discharge subsequently returned to the hospital where he was placed on ventilation again and presented with hypoxemia and dyspnea. The authors found that he had a "grossly enlarged right ventricle" and laboratory markers that indicated that the patient developed PH. van Dongen et al. [12] hypothesized that patients with COVID-19 pneumonia can develop "pulmonary hypertension and right ventricular failure," and that PH can arise from microvascular damage. A question that we will come back to later in this review is how fast PH and right ventricular failure can develop.

Clinical studies of multiple patients and subsequent meta-analyses provide many examples of RVD in association with COVID-19 and PH. Sud et al. [13] found that among their patients "with COVID-19 and significant myocardial injury… 17% had isolated right ventricular dysfunction, 17% had biventricular dysfunction." A later study by the same authors identified RV dilation as being prevalent among their patients [14]. The authors noted that patients presenting with RV dilation did not have differences in major comorbidities, inflammatory markers, or myocardial injury when compared to patients without RV dilation; however, these patients were more likely to experience renal dysfunction compared to those without RV dilation. RV dilation was strongly associated with mortality among patients with COVID-19 infection and myocardial injury.

Szekely et al. [15] conducted a large echocardiographic study in which a hundred patients were subjected to echocardiographic evaluation within 24 hours of admission. Among patients with abnormal echocardiograms, 57% presented with RV dilation. During hospitalization, 20% of patients experienced clinical deterioration, with 12 patients experiencing further deterioration of RV parameters.

Provencher et al. [16] speculated that the pandemic put those with pre-existing severe chronic PH at risk for development of cardiac problems, such as adaptive right ventricular hypertrophy or failure. The authors observed that patients with severe COVID-19 tend to develop "an atypical form of ARDS [acute respiratory stress syndrome] with significant dissociation between relatively well-preserved lung mechanics and severe hypoxemia." Similarly, Martínez-Mateo et al. [17] state that "right ventricular (RV) overload and RV failure are common" in patients who had COVID-19 and related pneumonia and developed ARDS; they also noted that four of their patients developed dilatation in the right cavities of the heart and that PH was absent among all six of their case studies. On the other hand, another study found that among their participants that had COVID-19 pneumonia, 41% had RV dilatation and 27% developed RV dysfunction [18]. While Mahmoud-Elsayed et al. [18] did not find a link between ventilation, RV dysfunction, and PH, the authors inferred that physicians could "limit positive end-expiratory

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pressure" upon identifying RV impairment to avoid hypercapnic acidosis, which could possibly induce pulmonary arterial hypertension and increased RV afterload. Mahmoud-Elsayed et al. [18] noted that "it is conceivable that a proportion of patients with RV dysfunction had undiagnosed thromboembolic disease" since not all of their patients underwent pulmonary angiography prior to their acute COVID-19.

Pagnesi et al. [19] found that among hospitalized non-ICU patients with COVID-19, presence of PH was associated with a higher rate of in-hospital death or ICU admission (41.7 vs 8.5%, $p<0.001$), while the presence of RVD was not (17.2 vs 11.7%, $p=0.404$). This is seen by the number of patients with PH who showed signs of severe infection (CXR lung damage, laboratory markers, oxygenation status, and noninvasive ventilation).

A recent meta-analysis review of studies of COVID-19 patients developing right ventricular impairment and pulmonary hypertension on mortality concluded that the consensus is that patients who develop PH or RVD through COVID-19 are more likely to die [20]. Similarly, a review by Cicco et al. [21] about cardiac imaging evaluation of COVID-19 patients concluded that RV hypertrophy may be caused by mechanical ventilation. The proposed mechanism is that mechanical ventilation can increase RV afterload, causing the RV to thicken in response to increased intrathoracic pressure. Cicco et al. [21] suggest that hypoxic pulmonary vasoconstriction is probably the main factor behind increased arterial pressure.

Tudoran et al. [6] noted that right ventricular global longitudinal strain (RV-GLS) was an echocardiographic parameter that provided a good prognosis for many heart failure-related outcomes. In their study to determine the presence and severity of PH two months after recovering from COVID-19 pulmonary infection the authors frequently documented incidences of PH and RVD in COVID-19 patients. These patients also presented with increased RV diameters and RV global longitudinal strain levels, which suggests RV enlargement and strain. Furthermore, tricuspid annular plane systolic excursion (TAPSE) levels were decreased in patients with PH and RVD, which along with the other echocardiographic markers suggest RVH.

The above studies consistently report RV dysfunction and dilatation occurring in association with COVID-19 and resultant PH. However, despite the recommendation that echocardiograph reports should include RV wall thickness along with other dimensions of the ventricle [22-24] none of them reported on the weight or wall thickness of the right ventricle, which would be necessary to determine if the reported RVD was accompanied by increased growth, i.e., hypertrophy. We've encountered one study that did report on wall thickness, by Lazzeri et al. [25]. These authors found that among COVID-19 patients requiring ventilation the average RV wall thickness of those with severe COVID-19 induced ARDS increased from 5.3 ± 0.5 to 5.9 ± 0.7 over 30 days, indicating RVH. Furthermore, increases in systolic pulmonary arterial pressures were observed in all patients, indicative of PH. Lazzeri et al. [25] suggested that such outcomes are caused by hypoxic vasoconstriction in lungs and that increased RV afterload resulting from mechanical ventilation may be the cause of the RVH. The report by Lazzeri et al. [25] provides direct support for our hypothesis that PH developed in association with COVID-19 may cause RVH, leading to a long-lasting RV dysfunction following COVID-19.

3.2. The Speed at which Pulmonary Hypertension Causes Heart Dysfunction in Animals

Prior to COVID-19, one might have expected RVH to develop slowly over periods of months or years in response to progressively developing PH caused by drugs or toxins, connective tissue disease, congenital heart disease, and other unknown causes [26]; however, COVID-19 causes a rapid, acute development of PH in many patients, as reviewed above. Patients may arrive at the hospital already in acute respiratory distress, exhibiting a recent development of PH in response to their COVID-19 infection. In serious cases of COVID-19 in which patients have needed to be placed on ventilators for days or weeks, the PH may be present for days or weeks. In many cases, also as described above, PH will cause RVD, and therefore the question arises as to how long RVD

 doi:10.20944/preprints202205.0030.v1

must be present for the increased stress to result in RVH. In contrast to the usual slow progressive development of RVH in response to chronic PH, van Dongen et al. [12] expressed the view that their COVID-19 patient had developed PH "over a much shorter time period than usually expected" accompanied by a "grossly enlarged right ventricle." The view that RVH can develop rapidly within days or weeks in response to acute PH is supported by various studies on animal models of PH in which the timing of the PH can be precisely controlled.

PH can be initiated by a variety of techniques.

Monocrotaline: In a study by Daicho et al. [27], PH was induced in rats by administration of monocrotaline, resulting in "marked myocardial hypertrophy and fibrosis" causing right ventricular failure within six weeks. Indeed, changes in echocardiographic parameters, ATP, and creatine phosphate were detected as early as four weeks after administration of monocrotaline [27].

Ligation or balloon catheterization of pulmonary artery: Mercier et al. (2013) induced chronic thromboembolic pulmonary hypertension (CTEPH) in piglets by ligation of left pulmonary artery; all of them developed PH within five weeks, with echocardiography showing RV enlargement and wall thickening, with progressive RV remodeling starting as early as 2 weeks post-ligation. Mean pulmonary artery pressure (mPAP) and total pulmonary resistance (TPR) was higher in the CTEPH group of piglets, compared to the sham group. Another study found that piglets with banded pulmonary arteries developed right ventricular hypertrophy by four weeks [28]. Luitel et al. [29] found significant changes in right and left ventricular structure and function of pulmonary artery banded mice within two weeks, with several changes taking place after three and seven days, respectively. Katayama et al. [30] induced right ventricular hypertrophy with an obstructing balloon catheter inserted into the main pulmonary artery and inflated twice a day for 2 to 2.5 hours for 4 consecutive days. The authors found that myocardial mass in the right ventricle increased after 4 days of this intermittently applied pressure overload; right ventricular weight was significantly higher in the balloon inflation group than those in the control group in measurements of wet heart (29.5 ± 1.2% versus 23.0 ± 1.0%; P< .0001) and dry heart weights (27.0 ± 2.0% versus 21.0 ± 1.1%; P< .0001).

Chronic hypoxia: Tabima et al. [31] found that mice exposed to chronic hypoxia for 10 days developed hypoxia-induced pulmonary hypertension (HPH), accompanied by RV hypertrophy, ventricular-vascular decoupling, and a mild decrease in RV contractile reserve. Similarly, Fried et al. [32] found that hypoxic rats exposed to low oxygen for 2 weeks exhibited RVH that they attributed to increased pulmonary vascular resistance as early as 5 days after the start of exposure. In addition, RV remodeling of treated rats is reflected by a significantly increased Fulton's Index value and reduced TAPSE when compared to the normoxia rats.

Spyropoulos et al. [33] conducted a study to determine which method of PH induction in rats is most like what humans undergo (two weeks of hypoxia, 28 days of MCT injection, and Sugen injection with placementin hypoxia for three weeks and normoxia for 1 week). All three models of PH induction had significantly higher RV systolic pressures when compared to normoxic controls and specifically, RV wall thickness was significantly greater in hypoxic compared to normoxic rats ($p<0.001$).

The above evidence would suggest that right ventricular hypertrophy can develop relatively rapidly, within a few days to weeks in response to pulmonary hypertension that might be caused by COVID-19. This would be consistent with what happened to the patient in Van Dongen's [12] case study in which the patient required ventilation (and probably had hypoxia) and was found to have developed pulmonary hypertension accompanied by RV dilation within 25 days of his initial admission to the hospital for COVID-19.

3.3. Future Investigations and Implications of the Hypothesis that COVID-19 PH causes RVH

The above considerations support the hypothesis that COVID-19 pneumonia can cause PH accompanied by changes in RV structure and function. The causal link be-

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tween COVID-19-induced PH and RVH in humans is circumstantial; however, rapid development of RVH in animals in response to acute activation of PH shows a causal relationship in these animal models. While this review describes numerous studies of humans in which RV dilatation in hospitalized COVID-19 patients has occurred in association with PH, only the study of Lazzeri et al. [25] has reported RV wall thickness, to provide direct support for hypertrophy and the hypothesis that a long-lasting after-effect of COVID-19 in some patients may be RVH caused by PH. More echocardiographic studies are needed to confirm the results by Lazzeri et al [25]. We would suggest that retrospective studies of electrocardiograms of patients that have been on a ventilator for two weeks or more (sufficient time for RVH to develop) should determine if the patient had PH, and if so, whether increases in RV size and wall thickness have occurred However, even with such confirmation, in a disease in which the virus SARS-CoV-2 is known to directly infect numerous tissues, including the heart, it may be difficult to prove a causal link between the PH and RVH in COVID-19.

RVH is considered a serious risk to cardiac health, often leading to heart failure and death. Sustained pressure overload on the right ventricle, as would occur if PH were long-lasting, can produce maladaptive irreversible remodeling of the right ventricle [34]. On the other hand, recent reports indicate that if the PH-related cause of RVH can be removed, the right ventricle is capable of a remarkable degree of recovery. In a mouse model, removal of the resistive cause of the RV afterload enabled RVH and exercise capacity to recover, whereas RV fibrosis recovered more slowly [35]. Typically, treatment of RVH when PH is present is directed at reducing the causal PH. There seems to be no consensus on treatments aimed directly at reducing or stopping the thickening of the walls of the right ventricle that occurs in RVH [36] or reducing the fibrosis that accompanies it as a therapeutic target [37].

In COVID-19 patients, treatments aimed at preventing a long-lasting PH due to microvascular damage in the lungs may prevent the development of an irreversible RVH. Thus, a goal of treatment of patients hospitalized with COVID-19 should be to reduce the occurrence of PH. Drugs that were used in targeted therapy for PH prior to the pandemic, including bosentan, sildenafil and epoprostenol, have been recommended for treating patients experiencing acute respiratory distress syndrome during COVID-19 and might therefore help to achieve that goal [38]. Another treatment that has been suggested for use during COVID-19 to reduce pulmonary arterial pressure and prevent right ventricular dysfunction is inhaled nitric oxide. Decreasing the occurrence of PH or reducing its duration may have beneficial effects on cardiac health following COVID-19.

Author Contributions: Conceptualization, J.L.R.; literature research, J.L.R. and S.H.Y.; writing—original draft preparation, S.H.Y.; writing—review and editing, J.L.R. and S.H.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest.

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