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SARS–CoV-2-mediated hyperferritinemia and cardiac arrest: preliminary insights

Prakash VasanthiDharmalingam[1], Vengadeshprabhu Karuppagounder[2], Kenichi Watanabe[3], Harry Karmouty-Quintana[4], Suresh S. Palaniyandi[5], Ashrith Guha[6] and Rajarajan A. Thandavarayan[6]

[1] Clone Gene Biosystems, Chennai, 600 018 Tamil Nadu, India
[2] Center for Orthopedic Research and Translational Sciences, Department of Orthopedics and Rehabilitation, Penn State College of Medicine, Hershey, 17033 PA, USA
[3] Department of Laboratory Medicine and Clinical Epidemiology for Prevention of Noncommunicable Diseases, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori Chuo-ku, Niigata 951-8510, Japan
[4] Department of Internal Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas, USA
[5] Division of Hypertension and Vascular Research, Henry Ford Health System, Detroit, MI 48202, USA
[6] Houston Methodist DeBakey Heart & Vascular Center, 6550 Fannin Street, Houston, TX 77030, USA

Severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), a pandemic that began in China, was first noted in December 2019. SARS–CoV-2 infects through the angiotensin-converting enzyme-2 (ACE-2) receptor and co-receptors. In the most severely affected patients, it can cause pneumonia and multiple organ failure leading to death. Reports describe high death rates resulting from cardiac dysfunction, a co-morbid condition in SARS–CoV-2 patients, while the primary cause and mechanisms remain unknown. Here, we attempt to review clinical reports of SARS–CoV-2 patients in order to provide insight into a possible mechanism that allows hyperferritinemia (the presence of excess iron-binding protein) to cause cardiac dysfunction in SARS–CoV-2 patients. Such insights are an important avenue towards understanding the mechanism of cardiac dysfunction in SARS–CoV-2 patients and developing remedies for the same.

Introduction

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2), the virus that causes corona virus disease (COVID-19), has imposed a serious threat to humans globally. Although it has caused mortality among all age groups [1], people over the age of 50 are more vulnerable. COVID-19 was first reported from a patient with symptoms of pneumonia in Wuhan, China in December of 2019 [2]. The zoonosis of COVID-19 was reported to have involved gene fusion between viruses infecting bats and snakes of wild origin, and the genome sequence of the virus in humans exhibits 96% identity to bat SARS-like corona virus [2]. Despite its zoonotic origin, SARS–CoV-2 is highly contagious in humans. COVID-19 patients exhibit clinical symptoms such as mild to severe pneumonia, acute respiratory distress syndrome (ARDS), acute cardiac dysfunction, renal injury and septic shock, sometimes causing death [3].

SARS–CoV-2 is a positive single-stranded enveloped RNA virus belonging to the β genus of coronaviruses (betaCoV) [4]. SARS-CoV-2 uses the transmembrane angiotensin-converting enzyme-2 (ACE-2) receptors that are expressed in cardiac tissues, blood vessels, gut, lung (particularly in type 2 pneumocytes and macrophages), kidney, testis and brain to infect host cells. Although SARS-CoV-2 infection is correlated with ACE-2 expression in *in vitro* analysis [5], the relationship between ACE-2 expression levels and susceptibly to SARS-CoV-2 infection and the mechanisms

Corresponding author:
Thandavarayan, R.A. (ramirthalingamthandavarayan@houstonmethodist.org)

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underlying multi-organ dysfunction remains unknown. Although other coronaviruses are known to cause multi-organ failure in hosts such as camels, cattle, cats and bats [6], the complications mediated by SARS-CoV-2 in humans hinder existing remedial measures [7–9]. In this review, we discuss preliminary insights into COVID-19- and iron-mediated acute cardiac injury, using data obtained from recent published clinical reports that may be useful in developing potential remedies.

Cardiac arrest in COVID-19 patients

It is hypothesized that SARS–CoV-2 mediates cardiac cell injury or inflammation through various mechanisms, including (i) supra-physiological immune inflammatory response and cytokine storm [10], (ii) direct viral invasion into cardiomyocytes, and (iii) oxidative stress and myocardial injury resulting from hypoxia or lung injury, and probably from reduced hemoglobin levels, which result from acute viral infection [11,12]. Nevertheless, innumerable factors could play a role in orchestrating these mechanisms, and each of these factors could be mediated by the COVID-19 virus and viral proteins in host cells. Initially, angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) were used as antiviral agents to combat viral infection into cardiac cells [13–15]. In addition to receptor blocking, however, ACEIs upregulate ACE-2 gene expression and the advice became that ACEI use should be discontinued in order to avoid any potential associated risk of SARS–CoV-2 infection; however, later findings have not supported this advice conclusively [16] (WHO/2019-nCoV/Sci_Brief/ACE-I/2020.1, https://apps.who.int/iris/handle/10665/332021). In fact, it has been advised that abrupt stopping of ACEI and ARB treatment may be more dangerous than the COVID-19 risk in high-risk patients with hypertension, heart failure or myocardial infarction [17].

Hyperferritinemia and cardiac arrest during SARS–CoV-2 infection

Searches for possible mechanisms of cardiovascular injury in COVID-19 patients led to reports of clinical data describing the occurrence of hyperferritinemia (an increase in the circulation of ferritin, an iron-binding protein), which is a typical indicator of viral or bacterial infection [18], combined with normocytic anemia (hemoglobin = 10.4 g/dL) and excess iron release in SARS–CoV-2-infected patients [19,20].

Ferritin is a ubiquitous cytosolic and mitochondrial iron-binding protein (existing as subunits H and L, and encoded by genes positioned on chromosomes 11q and 19q) in humans [21]. It stores iron in its nontoxic or biologically active form for vital cellular processes and helps to protect cellular macromolecules from the toxic effects of labile iron (Fig. 1). The H subunit of ferritin is highly expressed in the heart, whereas the L subunit is predominant in the liver.

The circulatory level of serum ferritin acts as a gold-standard prognostic marker for iron deficiency (hypoferritinemia) and iron overload (hyperferritinemia). Increased serum ferritin is strongly associated with a high risk of heart failure in coronary vascular diseases and with cardiovascular mortality [22–24]. The possible mechanisms through which hyperferritinemia induces myocardial dysfunction are: (i) induction of direct immune-suppressive [25,26] and pro-inflammatory effects [27]; and (ii) increased generation of hydroxyl radicals such as 8-hydroxydeoxyguanosine, 27-hydroxycholesterol [27], 4-hydroxynonenal [28] and malondialdehyde [29,30]. Ferritin H induces the expression of pro-inflammatory cytokines, and a study found that it also increases the expression of genes encoding IL-1β, IL-6, IL-12, and tumor necrosis factor α (TNF-α). Similar effects are also found in patients who have hyperferritinemic conditions, such as adult onset Still's disease (AOSD) patients with macrophage activation syndrome (MAS) [31]. In addition, the treatment of macrophages with Ferritin H induces increased expression of IL-1β and IL-12. Notably, both expression levels and extracellular release of IL-12 are significantly increased by ferritin H [32]. Another study found that the proinflammatory effects of Ferritin H occur through iron-dependent PKCζ/NFκB-regulated signaling in rat hepatic cells. In addition, in hepatic stellate cells, H-ferritin was reported to act as a proinflammatory cytokine via induction of the transcription factor NFκB [33].

It has been reported that about 50% of COVID-19 patients who have exceptionally high ferritin levels do not survive [18]. Moreover, reports suggest the occurrence of a cytokine storm in COVID-19 symptomatic patients that is mediated by hyperferritinemia and hyperferritinemia-mediated MAS. The cytokine storm involves an episode of overwhelming inflammation (caused by the initial expansion and activation of T lymphocytes and hemophagocytic macrophages) that is characterized by the excessive secretion of proinflammatory cytokines [34,35]. In addition, in a retrospective cohort study conducted in Wuhan, China, it was found that serum ferritin levels, as well as other factors such as high-sensitivity cardiac troponin I, were elevated in nonsurvivors of COVID-19 [36]. Notably, MAS, a life-threatening condition with high mortality rates, is usually associated with extreme hyperferritinemia [37,38]. Together, these findings suggest that cytokine storm might result in the destruction of healthy cardiac cells, provoking further cytokine production from uninfected cells and eventually causing autoimmune-mediated cardiac arrest/shock. However, numerous factors might influence the rates of mortality resulting from hyperferritinemia and MAS in COVID-19 patients.

Pathophysiology of hyperferritinemia in COVID-19 patients

A notable feature of hyperferritinemia (>3000 ng/mL), irrespective of its underlying pathology, is its association with increased mortality [27,39,40]. Ferritin gene expression is orchestrated at the transcriptional and post-transcriptional levels by many factors, including iron levels, T- and B-cell functions, cytokine release, chemokine production, lipopolysaccharides (LPS), prostaglandins, hormones, growth factors, second messengers, hyperoxia, hypoxia and oxidative stress [41,42]. Hyperferritinemia has been reported to exist in an array of clinical conditions such as AOSD, MAS, catastrophic serologic antiphospholipid syndrome (APS), septic shock and multiorgan dysfunction syndrome (MODS) [43], and these conditions (MODS, MAS and septic shock) have been well observed in COVID-19 patients [44–49]. Indeed, reports denote that macrophages are associated with the production and secretion of extracellular ferritin (H-ferritin) [50–52] (hence the MAS observed in COVID-19 patients) may be responsible for the higher serum ferritin levels seen in COVID-19 patients (elevated two fold

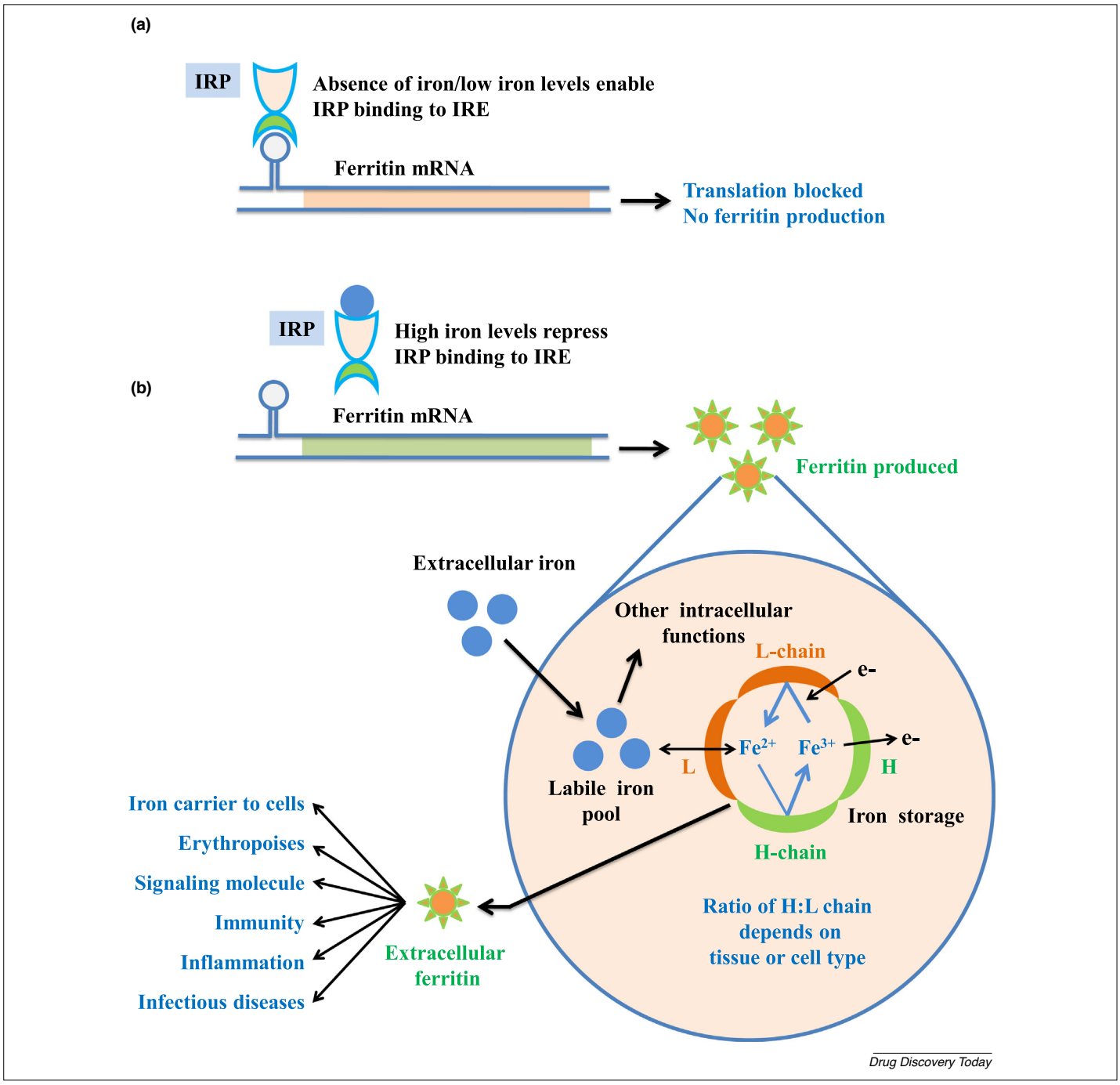

FIGURE 1

Physiology of ferritin. Schematic representation of ferritin production and its functions. Ferritin, an iron-storage protein, is expressed in the brain, liver, heart, kidney, bone marrow, skeletal muscle, spleen and lungs. **(a)** When levels of iron are low, iron regulatory proteins (IRPs) bind to RNA stem-loops within iron response elements (IREs) in the untranslated region of ferritin mRNA, thereby inhibiting the translation of this mRNA. **(b)** Conversely, high iron levels enable ferritin production by inhibiting the binding of IRPs to the RNA stem-loops of IREs in ferritin mRNA. Ferritin, a heteropolymer with 24 subunits has two types of chains (heavy and light). The ratio of heavy:light chain (H:L) is tissue- and cell-type-dependent and is altered during disease pathologies. The H-chain comprises di-iron binding sites with ferroxidase activity (Fe^{2+} to Fe^{3+}), whereas L-chain lacks mineralization activity.

in COVID-19 nonsurvivors than survivors) [48,53,54]. The same increases in the levels of macrophage-secreted ferritin have been associated with cardiovascular mortality [55] and the development of chronic coronary artery disease (CAD) [22].

In addition to the active secretion of ferritin from activated macrophages, further ferritin is released by the cellular death caused by the inflammatory reaction; hence the extreme inflammatory milieu that damages cardiac cells will eventually feed forward the cytokine storm. Upon release from cells, ferritin loses a proportion of its iron, thereby giving rise to extremely high levels of free iron in serum, which in turn will promulgate hyperferritinemia in other organs [56]. Notably,

the presence of circulating 'free iron' during severe inflammatory conditions can deteriorate the inflammatory reaction by inducing a marked pro-coagulant state, which is also observed in COVID-19 patients [56,57]. Such an increase in circulating free iron also induces changes in red blood cell (RBC) morphology, with fibrin leading to the generation of dense clots and eventually favoring cardiovascular stroke, myocarditis, cerebral stroke [57,58], and diffused intravascular coagulopathy, all of which are major complications in COVID-19 patients [59,60]. Moreover, the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukin-2 (IL-2) also induce ferritin synthesis in cells, including mesenchymal cells, hepatocytes and monocyte-macrophages [61], all of which can contribute to hyperferritinemia in SARS-CoV-2 patients.

COVID-19 is mainly characterized by fever, dry cough, fatigue and pneumonia, and these clinical symptoms are similar to those of hyperferritinemic syndromes [62]. However, the most severe form of COVID-19 is characterized by fever, hyperferritinemia and a hyper-inflammatory process, which may be responsible for the high rate of mortality [63]. Hyperferritinemia similar to that mediated by COVID-19 [53] is also reported in various autoimmune diseases, including systemic lupus erythematosus (SLS), multiple sclerosis and APS, while high levels of ferritin are reported in AOSD, MAS, septic shock and catastrophic APS [64].

In humans, hyperferritinemia has been reported to cause immunodeficiency [26]. Heavy-chain ferritin (H-ferritin) that is secreted by macrophages binds to T and B lymphocytes via its specific receptor, T cell immunoglobulin and mucin-domain-2 (TIM-2), and modulates intracellular signaling [25,50]. TIM-2 is expressed on cell types including B and T lymphocytes, liver cells [65], and erythroid precursor cells [66] and in brain cells [67]. Indeed, in *in vitro* conditions, such binding exerts immunosuppression by impairing T cell proliferation, B cell maturation and immunoglobulin production [25,68,69]. Initially, Broxmeyer et al. [70] suggested the regulatory role of ferritin in the production of granulocytes and macrophages, and it was further found that H-ferritin (but not L-ferritin) negatively regulates human and murine hematopoiesis *in vitro* and *in vivo*. H-ferritin also inhibits the proliferation of myeloid cells and the production of lymphoid lineage cells. Indeed, H-ferritin also suppresses the proliferation of T cells upon mitogenic stimulus and also impairs B cell maturation *in vitro* [71], while it has immunosuppressive function *in vivo* [72]. However, the mechanism underlying the ability of H-ferritin to mediate immunosuppression remains elusive and is believed to be mediated by the downregulation of CD2, a cofactor for lymphocyte stimulation [26], and probably by inducing IL-10 production in lymphocytes [73]. H-ferritin also induces apoptosis in hepatocyte cells by activating p53 [74], which in turn releases iron into phagocytic macrophages, leading to MAS as observed in COVID-19 patients with hyperferritinemia. Hence, hyperferritinemia-induced impaired generation of immune cells or immunosuppression can lead to the loss of disease tolerance and development of severe viral sepsis, to viral-sepsis-mediated inflammation and cytokine storm, and to the autoimmune destruction of tissues in hyperferritinemic COVID-19 patients [50] and might favor bacterial and other viral superinfections in COVID-19 Patients. Such development of autoimmune self-destruction of healthy cells is associated with the development of antibodies against ferritin and is also reported in patients with rheumatoid arthritis [75].

Severe COVID-19 may be considered part of the (heavy:light: heavy) HLH chain spectrum due to overlapping clinical features [76,77]. However, both laboratory and radiological differences between secondary HLH and severe COVID-19, which did not appear as part of the HLH spectrum, exist [78]. For better understanding, readers are invited to read the articles references cited above.

In macrophages, the role of ferritin is to cope with the normal or homeostatic turnover of senescent erythrocytes (10^{11} cells) and to assist in intracellular iron storage and the maintenance of iron availability for erythropoiesis. Any unexpected or sudden influx of supraphysiologic iron into macrophages will in turn lead to supraphysiologic ferritin gene expression, leading to extreme hyperferritinemia. Similarly, in cardiac tissues, viral-sepsis-mediated macrophage recruitment might also elevate iron uptake from damaged cardiac cells via inflammation, hyperferritinemia and sepsis, thereby causing cardiovascular dysfunction or cardiac arrest.

Extreme hyperferritinemia and cardiac arrest in COVID-19 patients: possible mechanisms

From the information obtained from published clinical reports, we speculate that the hyperferritinemia phenomenon observed in severe cases of COVID-19 is an extreme fatal form [18] that is not typical of hyperferritinemia due to infection alone: the initial infection-mediated hyperferritinemia is compounded by MAS and inflammation. In addition, Mitra et al. [19] observed the occurrence of leukoerythroblastic reactions, such as the presence of immature erythroids (nucleated erythroids) and immature myeloid cells circulating in the peripheral blood, as uncommon phenomena. Several studies note that in conditions where inflammation exists, RBC half-life is reduced: the RBC membrane is altered and structurally deformed and the expression of cellular adhesion molecules is increased in patients with sepsis [79,80]. In turn, all of these factors promote macrophage-mediated RBC phagocytosis and damaged hemoglobin turnover, which will eventually increase iron overload and hypoxia in tissues [27] and which might favor normocytic anemia during infectious conditions. In COVID-19, the presence of defective RBCs, hypoxia, inflammation-mediated turnover of RBCs [31], and macrophage activation after RBC phagocytosis could together induce extreme hyperferritinemia by: (i) promoting excess handling of iron cargo and (ii) increasing the release of iron into circulation by COVID-19-nonstructural-protein-mediated attack on the hemoglobin 1β chain. Therefore, the levels of free iron seen in COVID-19-mediated hyperferritinemia will be beyond physiologic levels, which will in turn induce pathological ferritin gene expression. In support of the above, reports denote that excess iron levels mediate the expression of genes encoding ferritin subunits, whereas low cellular iron levels obstruct the translation of stored ferritin mRNAs [81,82]. On the basis of previous studies, we hypothesize that virus-mediated hemoglobin 1β degradation results in chronic hypoxia, chronic hypoxia-mediated acidosis in tissues including the heart [83], iron-mediated oxidative stress and excessive cytokine generation. Chronic hypoxia accompanied by increased intracellular

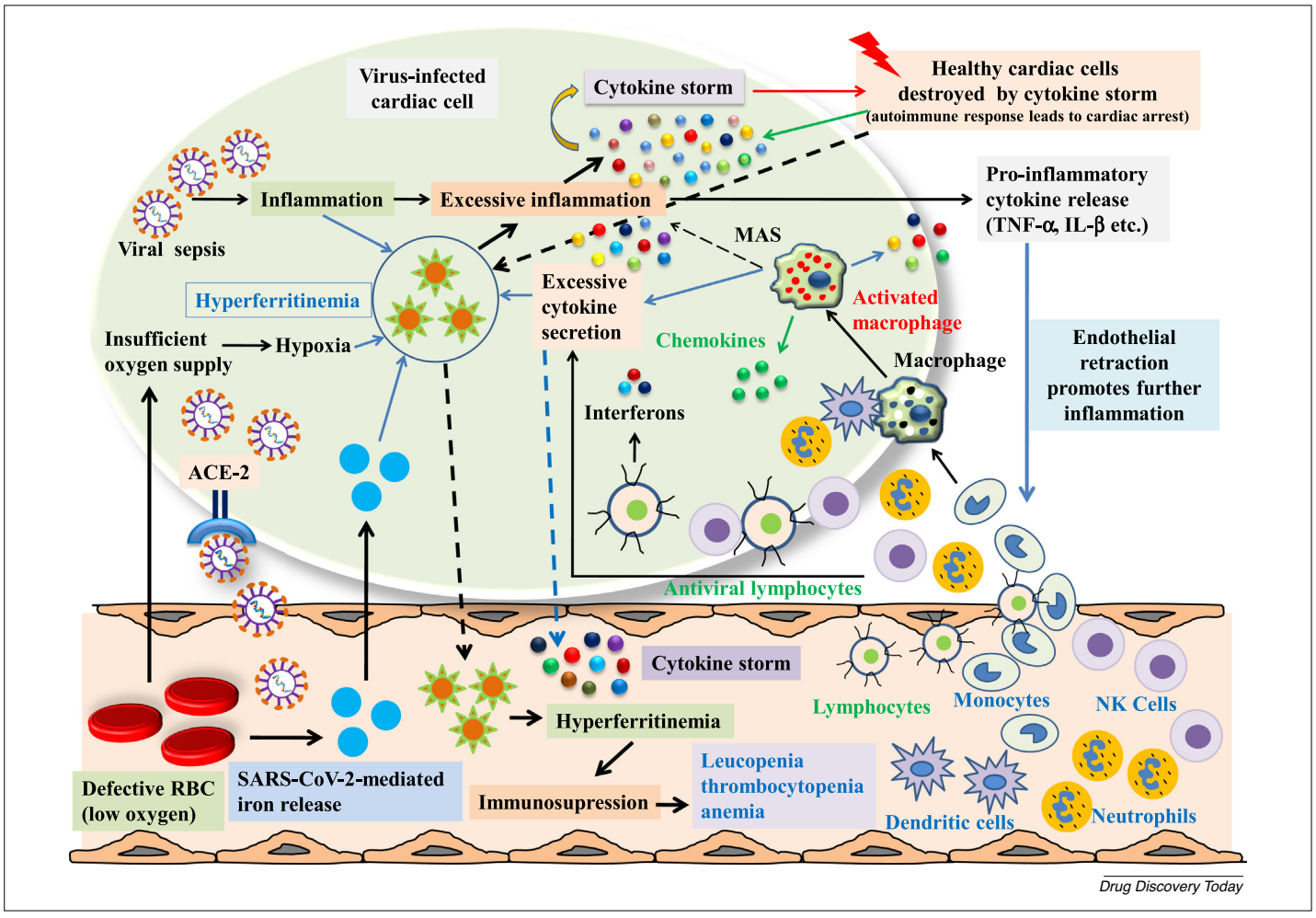

FIGURE 2

SARS–CoV-2-mediated hyperferritinemia and cytokine storm in cardiac cells. Initially, Angiotensin-converting enzyme-2 (ACE-2)-mediated viral uptake might induce inflammatory cell recruitment to infected cardiac cells, leading to the secretion of cytokines and chemokines. In addition, other factors such as COVID-19-mediated iron release from the 1β chains of red blood cells (RBCs), hypoxia, inflammation, oxidative stress, and cytokine generation may also mediate excess ferritin production, leading to hyperferritinemia. Hyperferritinemia and inflammation mutually increase each other, thereby contributing to excess hyperferritinemia and cytokine storm. Hyperferritinemia might eventually lead to immunosuppression and cytokine storm, which can cause damage to healthy cardiac cells, which in turn releases inflammatory cytokines, aggravating the cytokine storm and the autoimmune-mediated destruction of cardiac cells. IL-β, interleukin-β; MAS, macrophage activation syndrome; NK cell, natural killer cell; TNF-α, tumor necrosis factor α.

iron levels [84], oxidative stress [85], cytokines [27] and viral sepsis might augment increased ferritin gene expression [86,87] (Fig. 2).

By contrast, cytokine-mediated nitric oxide (NO) generation inhibits ferritin gene expression; this inhibition is mediated by binding of NO to sulfhydryl groups in the RNA binding domain and also by the formation of S-nitroso complexes with the thiols [88] of iron-regulatory proteins-1 (IRP1), which enable iron response element (IRE) binding activity [89,90]. Another report denotes that the presence of NO led to reduced IRP1 protein levels, which were correlated with the amount of NO produced [91]. However, we do not know whether the cytokines that are generated during COVID-19 infections activate NO generation or inhibit NO, thereby leading to hyperferritinemia. Clinical trials suggest that prolonged treatment with inhaled NO can lead to increased methemoglobin levels, while it is also reported that individuals with methemoglobin levels above 10% appear cyanotic and have impaired tissue oxygenation. This is because the Fe^{3+} heme in their methemoglobin is incapable of binding oxygen, and levels of methemoglobin above 30% may favor central nervous system (CNS) and cardiovascular symptoms [92]. Another report showed that if endothelium is exposed to methemoglobin for a prolonged period (16 h), the tissue accumulated large amounts of ferritin and subsequently underwent iron sequestration by this protein [93]. Similar phenomena were also observed in rodent lungs [94]. Thus, it seems that NO-mediated methemoglobin can help in chelating excess iron by favoring hyperferritinemia. Although it has been shown that endogenously produced NO inhibits H-ferritin synthesis [95], inhaled NO acts via methemoglobin to increase ferritin levels. Moreover, in *in vitro* conditions, NO also suppresses human hematopoiesis by inducing apoptosis in bone marrow progenitor cells [96]. Hence, our level of understanding of the usefulness of NO is very meager and warrants further extensive research.

In addition, hypoxia-mediated induction of ferritin gene expression is observed in mouse peritoneal macrophages [97] and rat hepatoma cells [84], and cardiac hypoxia resulted in elevated

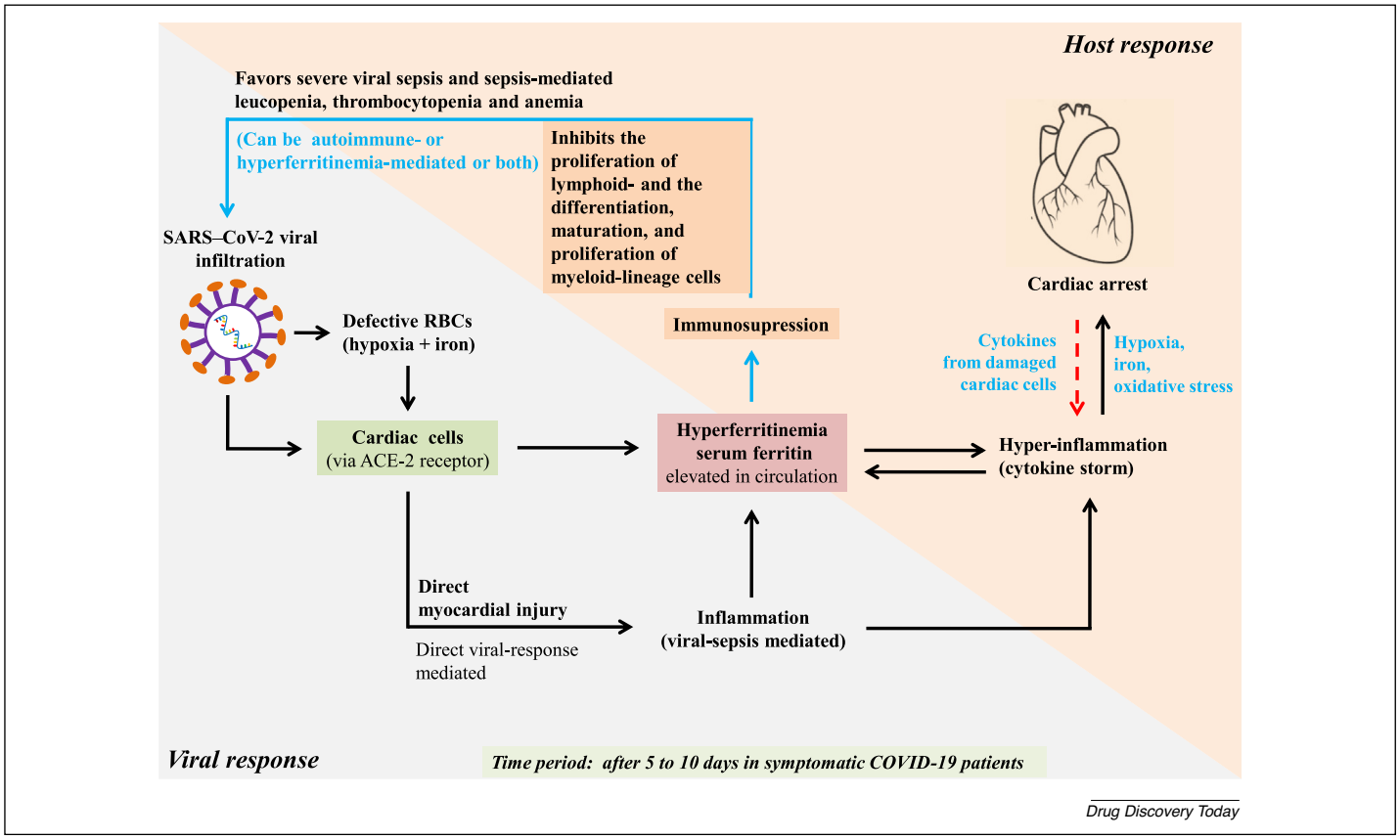

FIGURE 3

Hyperferritinemia-mediated cardiac arrest in COVID-19 patients: possible routes. ACE-2-receptor-mediated viral entry into hosts will induce inflammation via infiltration of immune cells to combat viral infection. Sepsis-mediated hyperferritinemia will be fueled by iron, hypoxia, oxidative stress, inflammation and macrophage activation syndrome (MAS), which will eventually result in excessive hyperferritinemia and cytokine storm. Cytokine storm will outplay protective inflammation for tissue repair and might lead to autoimmune-mediated destruction of healthy cardiac cells, promoting further cytokine secretion. Hyperferritinemia might inhibit immune cell differentiation and proliferation, causing leucopenia, thrombocytopenia and anemia; at the same time, cytokine storm may also result in autoimmune destruction of immune cells, favoring immunosuppression and eventually causing viral sepsis and cardiac dysfunction or heart failure. The increase in hyperferritinemia might inhibit the isotype class switching of immunoglobulins IgM to IgG, IgA or IgE causing asymptomatic COVID-19 infection (1 to 10 days) to symptomatic COVID-19 condition thereby causing immunosupression favoring bacterial and other viral superinfections, along with COVID-19.

cardiac ferritin levels [98]. Therefore, we speculate that chronic hypoxia, associated excess iron levels resulting from hemoglobin 1β chain damage, abnormal turnover of erythrocytes [19], acidosis, iron-mediated oxidative stress, cytokine generation, iron accumulation from inflammatory cell death, and MAS might collectively trigger extreme hyperferritinemia and excessive cytokine storm in the cardiac tissues of COVID-19 patients. Cytokine-storm-mediated inflammatory milieu would damage healthy cardiac cells, which would in turn aggravate inflammatory cytokine production as a part of the cytokine storm, leading to sudden cardiac arrest in COVID-19 patients [99–101]. Extreme hyperferritinemia might also: (i) favor excessive cytokine secretion, (ii) cause H-ferritin-mediated immunosuppression by inhibiting the proliferation of lymphoid cells and the differentiation, maturation, proliferation of myeloid lineage cells, thereby causing immunosupression and (iii) favor higher SARS-CoV-2 viral proliferation and other bacterial, viral superinfections and sepsis in cardiac cells and other tissues [102–104] (Fig. 3).

In addition, if COVID-19 nonstructural proteins attack and damage the 1β chain of hemoglobin (releasing free iron) while binding porphyrin, this would entail the loss of metalloporphyrin from the body and would eventually cause perturbations in metalloporphyrin homeostasis [105]. Notably, metalloporphyrins [iron- (hemin) and Sn-protoporphyrin] have been shown to act as immunostimulatory agents *in vitro* [106,107]. In addition, a report by Burt et al. [108] showed that inhibition of hemeoxygenase (HO-1) by tin-mesoporphyrin (SnMP) in peripheral blood mononuclear cells (PBMCs) leads to increased anti-viral T cell activation and to the generation of a higher proportion of effector memory T cells with increased capability to secrete interferon (IFN)-γ and granzyme B. Moreover, exposure of these cells to SnMP increased anti-viral T cells 15-fold. Hence, COVID-19-mediated attack on the 1β chain of hemoglobin would cause defective or suppressed immunogenic generation of anti-viral effector T cells and memory T cells, leading to defective adaptive immune defense / immunodeficiency. In support of the above, about 82.1% of COVID-19 patients have reduced lymphocyte counts [12,109,110] due to unknown factors or mechanisms [102]. Similarly, a very recent report suggests that asymptomatic individuals who have a poor or weakened adaptive immune system are much more prone to progress to symptomatic COVID-19 illness [111]. In support of

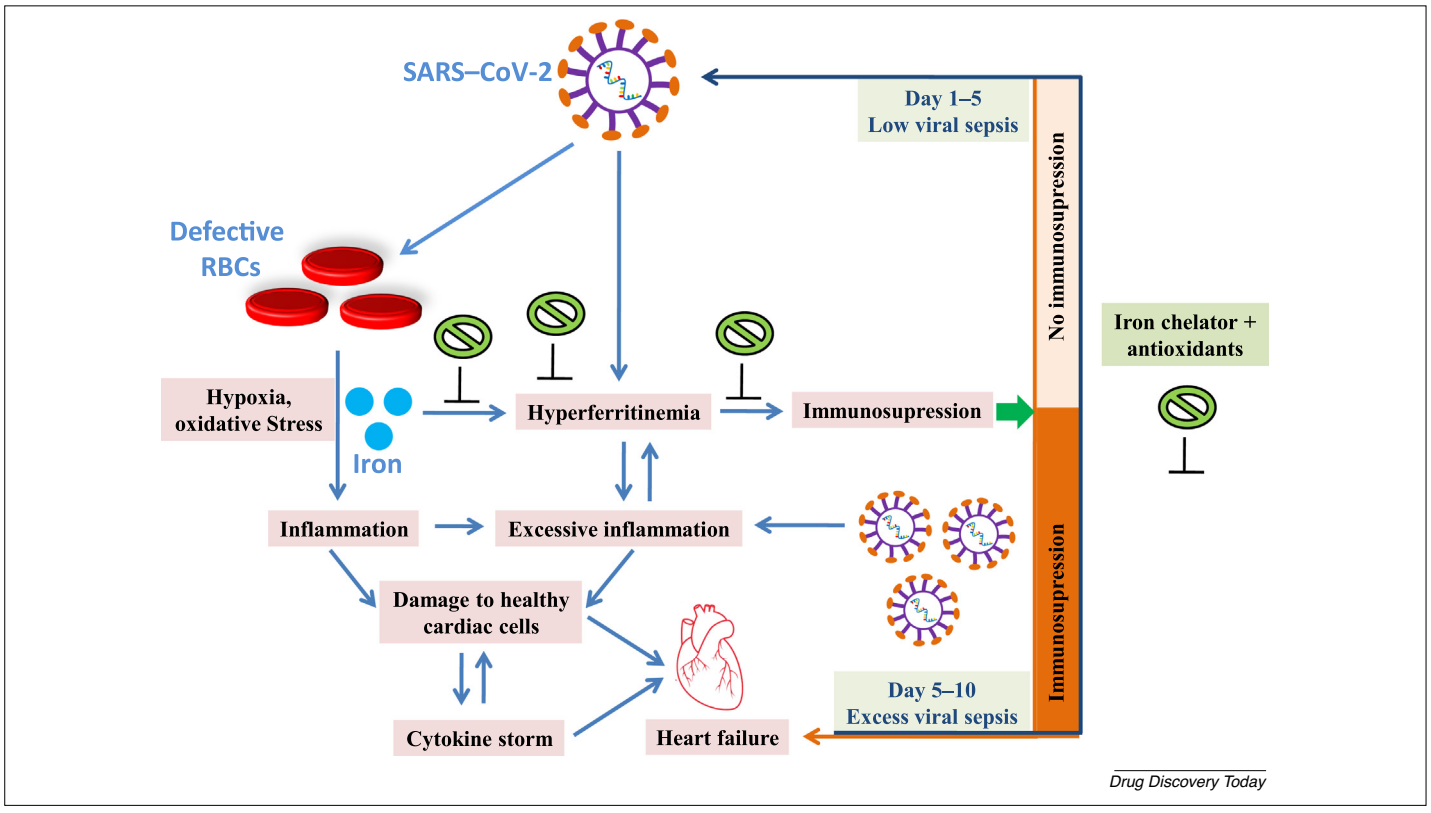

FIGURE 4

Therapeutic perspectives: using iron chelators to combat hyperferritinemia. During the early days of (days 1–5) asymptomatic COVID-19 infection, there is no protective inflammation to combat viral proliferation and tissue repair in cardiac cells, but the levels of hyperferritinemia and excessive inflammation will be meager or solely mediated by viral infection. As the infection progresses (days 5–10), however, the amount of viral sepsis and inflammation will be higher and might result in hyperferritinemia [fueled by iron release, hypoxia, oxidative stress, cytokine release, and macrophage activation syndrome (MAS)] and hyperferritinemia can mediate excessive inflammation. Excessive inflammation, in turn, may cause damage to healthy cardiac cells, promoting further cytokine secretion eventually leading to cytokine storm and cardiac shock/arrest. Hyperferritinemia can be reduced by iron chelators (deferriprone and desferasirox, which degrade ferritin). By reducing hyperferritinemia, events such as hyperferritinemia-mediated immunosuppression and excessive inflammation can be prevented and immune cells may be able to combat viral sepsis by themselves.

the above, some COVID-19 patients exhibit hypoxia despite having well-preserved lung compliance and/or hypoxia preceding lung injury or pneumonia, neither of which are typical of ARDS [112,113]. We speculate that these phenomena can be explained by a reduction in the oxygen-carrying ability of hemoglobin (with intact α1, α2 chain and β2 chain) in COVID-19 patients. Notably, the clinical presentations of COVID-19-associated hyperferritinemia and thrombocytopenia are similar to those of systemic lupus erythematosus disease (SLE), hemophagocytic lymphohistiocytosis, macrophage activation syndrome and AOSD [41].

Reduced iron levels have also been reported in COVID-19 patients [12], although it may be possible that blood for these analyses was collected only from symptomatic COVID-19 patients, i.e. between 14–20 days after asymptomatic incubation [114]. During the asymptomatic period, hypoxia, oxidative stress and cytokines can lead to ferritin induction, which could lead to the reduced hemoglobin (normocytic anemia) and reduced iron levels (can be due to ferritin mediated iron uptake) seen in clinical samples of 99 patients with COVID-19 [12]. In addition, it is possible that the supraphysiologic iron released by COVID-19-mediated RBC 1β chain destruction can be released into circulation and accumulated in tissues such as cardiac cells during the asymptomatic COVID-19 incubation period, favoring ferroptosis and cardiomyocyte cell death and cardiovascular damage [115,116]. Moreover, other factors such as cardiomegaly, cardiac myocyte injury, lymphocytic pericarditis, and lymphocytic myocarditis were found to be involved in cardiac dysfunction in COVID-19 patients [117]. We also speculate that these phenomena could be applicable to other forms of organ dysfunction in COVID-19 patients.

Conclusion remarks and future perspectives

Our review of the literature indicates a plausible pathophysiological role of hyperferritinemia-mediated cardiovascular damage in COVID-19 patients. Moreover, it has been reported that increasing L-ferritin to compensate H-ferritin can help in reducing pro-inflammatory cytokine levels, multi-organ dysfunction and high mortality rates in a murine model of sepsis. Such regulation of L-ferritin and H-ferritin levels could be considered in COVID-19 [118]. In addition, we propose that the use of iron chelation agents such as deferoxamine (DFO) (alone or synergistically with antioxidants to mitigate iron-induced oxidative stress) [119–122] or deferriprone and desferasirox (which degrade ferritin) [123,124] might help to reduce

hyperferritinemia while scavenging excess iron (Fig. 4). Furthermore, we believe that the development of modified or improved iron chelators that can significantly enhance ferritin degradation and iron chelation, while simultaneously providing antioxidant capacity and reducing the iron-chelator-mediated cytotoxicity of macrophages, might be highly beneficial in mitigating COVID-19-mediated pathology [105,125,126]. However, we suggest that the use of iron chelators should be regulated, because it might affect the homeostatic process that activates the hemeoxygenase-1 enzyme by limiting the availability of basal level iron that is essential for iron-trafficking-mediated heme production in cells. Notably, hemeoxygenase production is required for the generation of antiviral interferons in our body (IFNα/β) [127].

Simultaneously, management of hypoxia to avoid hypoxia-mediated hyperferritinemia might also help to minimize or at least reduce hyperferritinemia- and cytokine-storm-mediated cardiovascular dysfunction and arrest in COVID-19 patients. Finally, we point out that these are hypothetical insights and have not been proved or observed by laboratory experimental models involving COVID-19 virus infection. We recommend further focused research using suitable experimental models and clinical samples that will help us to understand the impact of hyperferritinemia in the cardiovascular health, morbidity and mortality of COVID-19 patients.

Conflict of interest

None.

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