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PERSPECTIVES | *Integrative Cardiovascular Physiology and Pathophysiology*

COVID-19 and hypertension: is the HSP60 culprit for the severe course and worse outcome?

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Jakovac H. COVID-19 and hypertension: is the HSP60 culprit for the severe course and worse outcome? *Am J Physiol Heart Circ Physiol* 319: H793–H796, 2020. First published September 4, 2020; doi:10.1152/ajpheart.00506.2020.—The 60-kDa heat shock protein (HSP60) is a chaperone essential for mitochondrial proteostasis ensuring thus sufficient aerobic energy production. In pathological conditions, HSP60 can be translocated from the mitochondria and excreted from the cell. In turn, the extracellular HSP60 has a strong ability to trigger and enhance inflammatory response with marked proinflammatory cytokine induction, which is mainly mediated by Toll-like receptor binding. Previous studies have found increased circulating levels of HSP60 in hypertensive patients, as well as enhanced HSP60 expression and membrane translocation in the hypertrophic myocardium. These observations are of particular interest, since they could provide a possible pathophysiological explanation of the severe course and worse outcome of severe acute respiratory syndrome coronavirus 2 infection in hypertensive patients, repeatedly reported during the recent coronavirus disease 2019 (COVID-19) pandemic and related to hyperinflammatory response and cytokine storm development during the third phase of the disease. In this regard, pharmacological inhibition of HSP60 could attract attention to potentially ameliorate inappropriate inflammatory reaction in severe COVID-19 patients. Among HSP60 antagonizing drugs, mizoribine is the most intriguing, since it is clinically approved and exerts antiviral activity. However, this topic requires to be further scrutinized.

COVID-19; HSP60; hypertension; mizoribine; SARS-CoV-2; severity

During the recent coronavirus disease 2019 (COVID-19) outbreak, hypertensive patients emerged as a high-risk group prone to develop acute respiratory distress syndrome (ARDS) and potentially lethal cardiac injuries consequent to infection (6, 25). Severe clinical picture and increased mortality of these patients are still being reported and documented, but the underlying pathophysiological mechanism by which hypertension aggravates COVID-19 presentation remains unclear. Initially, the main guilt was being almost exclusively attributed to the widely used renin-angiotensin system (RAS)-modulating antihypertensives, more precisely to angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), relying on the previous findings showing the ability of these drugs to induce overexpression of angiotensin-converting enzyme 2 (ACE2), which is exploited by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a receptor for cell entrance (2, 20), but remaining without sufficient well-argued clinical evidence (22). However, in addition to mediating viral entry, ACE2 has been known as an anti-

inflammatory and proregenerative molecule, and intensive research is being conducted to take advantage of these desirable effects during SARS-CoV-2 infection (7). Although there is still a brisk debate on the relevance of ACE-Is and ARBs as harmful agents, recently, several well-designed clinical studies and meta-analysis showed just the opposite; among the cohorts of hypertensive COVID-19 patients, those receiving the incriminated drugs had a lower rate of severe disease and lower all-cause mortality rate (10, 15, 26). Also, abrupt discontinuation of ACE-Is or ARBs in cardiovascular COVID-19 patients was leading to clinical deterioration and worse outcomes (15). These findings, by the Copernican turn, directly point to RAS-modulating drugs as potentially protective agents and highlight the importance of ACE2 as a producer of anti-inflammatory heptapeptide angiotensin-(1–7) during SARS-CoV-2-induced inflammation (7), but at the same time deprive us from any plausible explanation of hypertension supported severe COVID-19 manifestations. Currently, the association between hypertension and the severity of SARS-Cov-2 infection remains only an observational phenomenon without established causation. In hypertensive patients with fully developed metabolic syndrome, predisposition to a more severe course of the disease can be at least partially attributed to the lack of anti-inflammatory insulin signaling and the hyperproduction of inflammatory adipokines, which generate a state of persistent low-level systemic inflammation (1). How hypertension, per se, could worsen the course and outcome of SARS-CoV-2 infection has yet to be clarified by further experimental and clinical data. Because dissecting of the enigmatic COVID-19 pathophysiology focuses mainly on the altered immune responses, some authors suggest that the causative mechanism could most likely be immune mediated (9). In that context, attention is drawn by the previously established association between hypertension and increased plasma concentration of the heat shock protein 60 (HSP60) (16, 17, 19). HSP60 is mitochondrial chaperone essential for the proper function of mitochondrial enzymes involved in oxidative phosphorylation, playing thus an important role in energy homeostasis. Early studies on animal models showed its protective function during myocardial injuries, mostly mediated by preserving mitochondrial integrity (3). However, when translocated from the mitochondria and released from the cells, HSP60 becomes a pathophysiological mediator of various pathological processes, primarily because of its pronounced immunogenic ability (8, 19). Namely, extracellular HSP60 shows features of the canonical damage-associated molecular pattern (DAMP) and, as a “danger signal” through the widely distributed Toll-like receptor (TLR) family, activates the NF- κ B pathway, stimulating con-

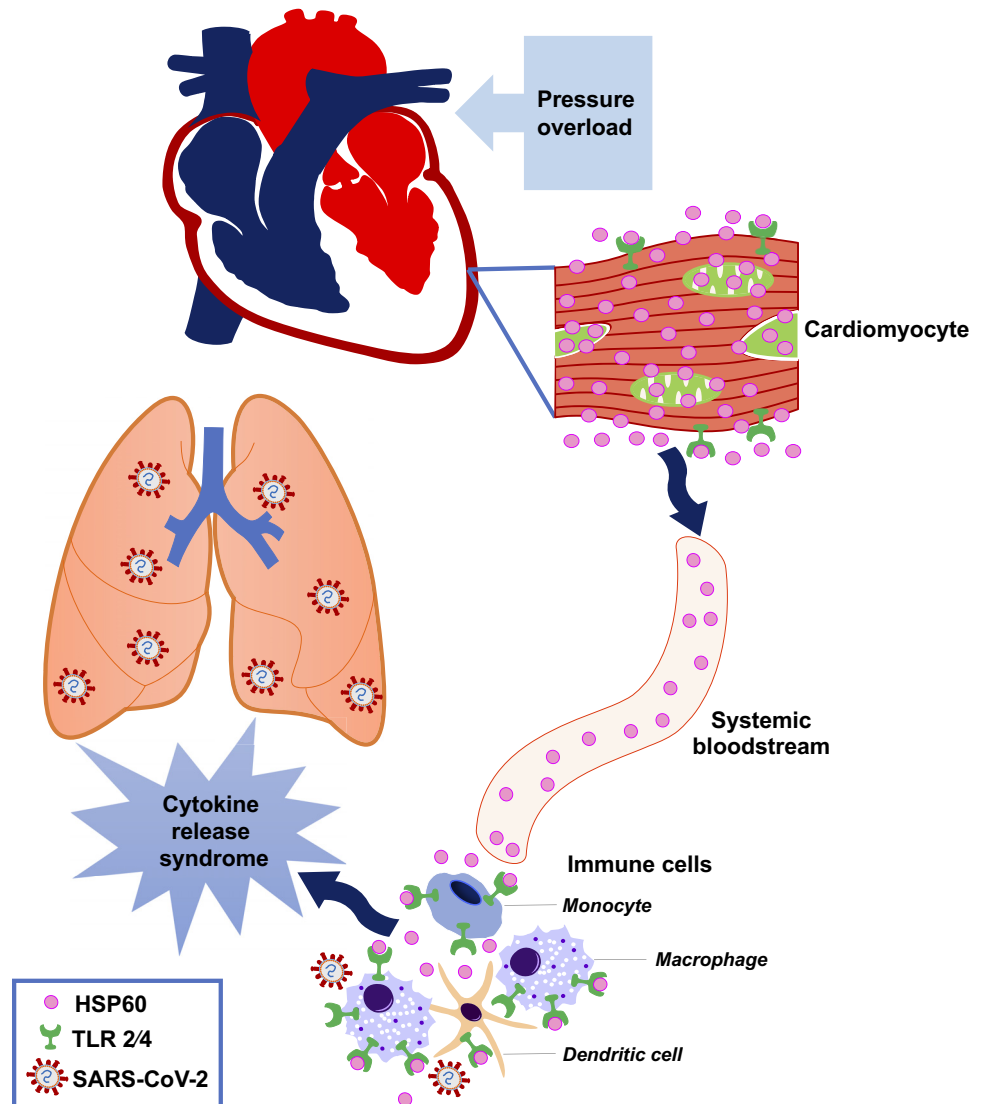
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sequently the proinflammatory cytokine release (8, 12). Therefore, it is reasonable and justified to hypothesize that preexisting high plasma HSP60 concentrations in hypertensive patients could contribute to the development of the cytokine release syndrome, which is the major executive mechanism responsible for ARDS and heart failure development during the third (hyperinflammatory) phase of the COVID-19 disease (20), and therefore represents a major concern for clinicians. Unpredictability and tremendous variability of manifestations during this phase are attributed to the host responsiveness (20) and could be influenced by preexisting levels of plasma HSP60. It should be pointed out here that population-screening studies found significantly elevated levels of circulating HSP60 even in the subjects with “borderline” hypertension (17), in whom high arterial blood pressure clinically can often be overlooked and undiagnosed. Also, HSP60 has been shown to initiate a proatherogenic immune response during the early, still reversible, stage of atherogenesis (19). These findings have led some authors to suggest elevated plasma HSP60 concentration as a predictor of atherosclerotic cardiovascular disease (17). Interestingly, HSP60 expression seems to correlate positively with

RAS activity, since animal studies showed that treatment with the ACE-I trandolapril attenuates HSP60 induction in the failing heart after acute myocardial infarction (23), whereas the ARB candesartan was found to downregulate HSP60 transcription and abolishes brain microvascular inflammation in spontaneously hypertensive rats (28). These data are in line with the recently observed benefit of ACE-I and ARB continuation in SARS-CoV-2-infected hypertensive patients (10, 15, 26).

After the initial tissue damage induced by SARS-CoV-2, DAMPs, such as HSP60, can be released from any affected cells in the circulation, adding to the preexisting ones. Exceeding the certain critical level of circulating DAMPs during infection may be responsible for prolonged hypercytokinemia, which maintains a systemic hyperinflammation resulting with damage to distant organs and multiorgan failure syndrome, despite effective viral clearance (20). In turn, DAMPs released subsequently to cytokine-driven tissue injury can perpetuate inflammation, establishing thus the vicious cycle of inflammatory self-amplification. The proposed critical level of circulating DAMPs, able to initiate such a sequence of events, is theoretically determined by the extent of the viral-induced

Fig. 1. The proposed role of 60-kDa heat shock protein (HSP60) in hypertensive coronavirus disease 2019 patients. As a part of the adaptive response to increased energy demands caused by long-term pressure overload, cardiomyocytes overexpress mitochondrial HSP60, which in turn is translocated to the sarcolemma and, as assumed, released in intercellular spaces (3). Released HSP60 binds to cardiac Toll-like receptors (TLRs), and, providing permanent local proinflammatory signals, makes the heart more vulnerable during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The resulting inflammatory milieu also favors endothelial damage, thus contributing to the thrombotic tendency. Extracellular cardiac HSP60 may enter the systemic bloodstream and, as a canonical “danger signal,” through the TLR2/4 stimulate immune cells to produce proinflammatory cytokines, resulting in a systemic proinflammatory state as a consequence of hypertension. During SARS-CoV-2 infection, overall proinflammatory cytokines presumptively produced in response to high plasma HSP60 in hypertensive patients more likely can exceed the level critical for the emergence of cytokine release syndrome, which in turn leads to acute respiratory distress syndrome, acute cardiac injuries, endotheliopathy, thrombogenesis, and multiorgan failure syndrome.



injury and concentration of preexisting circulating DAMPs, wherein elevated HSP60 in hypertensive patients could be a decisive factor. On the trail of that, plasma HSP60 concentrations were found to correlate positively with acute lung injury and systemic inflammatory response in patients with severe nonpulmonary trauma (14). On the other hand, our recent study (3) found striking overexpression of HSP60, TLR2, and TLR4 in the myocardium of subjects with concentric left ventricular hypertrophy, which represents a common adaptive response to long-term hypertension. Such a strong induction of the mitochondrial chaperone is in accordance with the increased energy demands of the burdened ventricle in an effort to maintain appropriate cardiac output. Nevertheless, accumulated HSP60 showed membrane translocation and interaction with TLRs in the hypertrophic myocardium, which, along with accompanying NF- κ B activation, strongly suggest that HSP60 is released from hypertrophic cardiomyocytes (3). That possibility is also supported by previous in vitro studies showing active secretion of HSP60 from cardiomyocytes under noxious stimuli (19). The resulting constitutively proinflammatory milieu in the tissue of pressure-overloaded heart could accelerate and amplify acute cardiac injury directly, but also by facilitating endothelial damage leading to the thrombotic events, which appears to be a common finding in severe COVID-19 patients (5, 18, 27). It is also worth mentioning that in vitro studies showed the arrhythmogenic effect of TLR4 activation (13), which can be HSP60 mediated, suggesting special caution when (hydroxy)chloroquine must be administered to hypertensive COVID-19 patients. Although no data on the effect of (hydroxy)chloroquine on HSP60 expression are available so far, it can be assumed that inhibition of autophagic/mitophagic clearance by these drugs (4) could even favor HSP60 overexpression. Chloroquine and hydroxychloroquine interfere with endosomal TLRs7/8/9 that are responsible for virus-driven inflammation but not with TLRs2/4 that bind HSP60 and other DAMPs (4). This at least partially may explain inconsistent efficacy of (hydroxy)chloroquine treatment among severe COVID-19 patients, suggesting that those with hypertension could be weaker responders. However, further thorough clinical stratification of COVID-19 patients receiving hydroxychloroquine or chloroquine is required to confirm this presumption.

According to the foregoing deliberation, HSP60 inhibitors could be considered as potentially beneficial agents for hypertensive patients infected with SARS-CoV-2. In that regard, mizoribine, an imidazole nucleoside with potent immunosuppressive activity, is the most promising Hsp60-modulating compound, since it is clinically approved, and, very importantly, it also showed antiviral activity against SARS-CoV-1 (11, 21). Other substances that can antagonize HSP60 activity, but are not clinically approved, include epolactaene, myrtucommulone A, stephacidin B, and gold porphyrins (11, 24).

It can be concluded finally that all available data taken together can give rise to the assumption that heart under increased workload, adapting to increased energy requirements, becomes a source of plasma HSP60, which in turn generates a systemic proinflammatory state responsible for the more severe COVID-19 manifestations in hypertensive patients (Fig. 1). However, further basic and clinical studies are needed to confirm the proposed mechanism.

DISCLOSURES

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