The clinical rationale of Sacubitril/valsartan for therapeutic treatment in Sars-CoV-2

Francesco Ferrara[1] and Antonio Vitiello[1]

[1]Azienda Unità Sanitaria Locale Umbria 1

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Abstract

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Clinical aspects SARS-CoV-2 (COVID-19) infection

A viral epidemic caused by a new coronavirus SARS-CoV-2 (COVID-19) began in Wuhan (China) in November 2019. The epidemic quickly became a global pandemic (1). Knowledges of this viral infection is evolving rapidly, to date there are still no direct antivirals or effective vaccines and therapeutic treatments are on an empirical basis. At the time of writing this article, 10.7 million infected people and about 516,000 deaths are reported. (2) SARS-CoV-2 is a family of RNA viruses capable of infecting humans and causing severe respiratory tract infections that can be fatal in some cases. (3) Studies have shown that SARS-CoV-2 has about 80% of the SARS-CoV-like genome responsible for the 2003 outbreak. (4) SARS-CoV-2 penetrates into cells using the S protein via the angiotensin 2 conversion enzyme receptor (ACE-2) on the cell surface, which is widely present in the epithelial cells of the respiratory mucosa, (5). ACE-2 is also a conversion enzyme with a key role in the renin-angiotensin system (RAS). Clinical experts and scientists have described SARS-CoV-2 infection in three stages: the first asymptomatic or mildly symptomatic, the second moderately severe characterized by a pulmonary inflammatory state, the third very severe stage characterized by a generalized inflammatory state affecting all tissues causing multi-organ dysfunction. (6) In the most severe stages of infection, COVID-19 lung lesions are characterised by diffuse alveolar damage with irregular inflammatory cellular infiltration consisting of the presence of monocytes, macrophages and lymphocytes infiltrating the lung interstitium, and presence of intravascular thrombosis. (7). Severe inflammatory pulmonary infiltration prevents the exchange of alveolar gases, moreover, the most serious cases develop significant cardiovascular morbidity (8), (9). In this last direction, in fact data that have recently emerged do not only identify COVID-19 viral infection as a respiratory disease and risk of acute respiratory distress syndrome but also with acute myocardial damage that can be a critical component in the development of serious complications. These aspects are further confirmed by studies that show that patients with a history of cardiovascular disease are at increased risk of COVID-19 complications. (10) In fact, in a recent study (11) it was found that 77% of the deceased patients developed acute myocardial damage, other studies confirm these data. (12) (13) Some pathophysiological bases have been hypothesized, one of which is that the phenomenon of the "cytokinic storm" (14) which occurs in the most severe stages of COVID-19 infection causes myocarditis which is the cause of acute heart failure, in addition, TNF-α and some other pro-inflammatory cytokines are capable of inducing typical cellular modifications of the decompensated heart, such as down-regulation of the sarcoplasmic reticulum ATPasica calcic pump (15), or decoupling of the beta-adrenergic receptors from activation of cyclic intracellular AMP (16) or death of heart cells.

Cytokinic storm and heart failure

The most severe stages of COVID-19 infection are characterized by a hyperinflammatory state caused by a cytokinic storm. The term indicates the role of the immune system in producing an uncontrolled and generalized inflammatory response (17). This uncontrolled inflammatory response causes severe lung injury and cardiac damage (18) (19).

The data clearly indicate that the uncontrolled and sudden release by immuno effector cells of large amounts of pro-inflammatory cytokines (IFNα, IFNγ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGF-β) (20) and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3, CCL5) causes the aberrant systemic inflammatory response causing multi-organ dysfunction (21)(22)(23)(24) and cardiac damage. Pro-inflammatory cytokines are particularly responsible for cardiac damage. Several studies show that TNF-α plays a central role in myocardial contractility depression through various time-dependent mechanisms. The cardiodepressant effect of TNF-α is the consequence of a signaling dependent on nitric oxide synthase (NOS), a high concentration of Nitric Oxide (NO) in fact leads to (25) to an inotropic negative effect (26) and to deep systolic and diastolic dysfunction (27). TNF-a also induces apoptosis in cardiac myocytes (28), which contributes to thinning of the left ventricular wall (29)(30). At the molecular level, sustained overexpression of TNF-a activates both the intrinsic and extrinsic apoptotic pathways and leads to progressive loss of antiapoptotic proteins (31).

IL-6 is a powerful mediator of myocardial depression, which in turn enhances the cardiodepressant effects of TNF-a and IL-1 (32). The inotropic negative effect of IL-6 is the result of JAK2/STAT3mediated activation of iNOS (33). IL-1 also produces prolonged decrease in myocardial contractility (34) Finally IL-18 stimulates proinflammatory cytokines with known cardiodepressant effects, i.e., TNF-a, IL-1a, IL-1b, IL-6 (35)(36), and also IL-18 has been shown to induce NO synthesis (36), which mediates myocardial dysfunction. Finally through different mechanisms of action the proinflammatory cytokines described above mediate contractile dysfunction and myocytic cardiac apoptosis with cardiac damage.

Natriuretic peptide system, biological effects

Natriuretic peptides are a family of structurally related hormonal factors. Atrial natriuretic peptide (ANP) and type B natriuretic peptide (BNP) are secreted by the atria and cardiac ventricles. Type C natriuretic peptide (CNP) is the most highly expressed natriuretic peptide in the brain, but is also highly expressed in chondrocytes and endothelial cells. Neutral neprilisin endopeptidase (NEP) is the enzyme that metabolizes natriuretic peptides. Natriuretic peptides mediate different physiological effects through interaction with specific guanylyl cyclase (GC) receptors that cause intracellular cGMP production. The main physiological effects are natriuresis / diuresis and peripheral vasodilation, inhibition of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) but other important biological functions have been highlighted in recent times. In particular, some studies have demonstrated an antifibrotic and anti-inflammatory action associated with natriuretic peptides. The natriuretic peptide type C (CNP), a member of the natriuretic peptide family, by selective binding to the transmembrane receptor guanylyl cyclase (GC)-B, mediates different biological effects in various organs. (37) CNP is expressed in a wide variety of tissues, such as the vascular endothelium, heart, bones and adrenal glands. (38) (39)(40)(41) CNP plays an important role in the regulation of local vascular tone, and has been shown to have mainly cardioprotective, antihypertrophic (42) and antifibrotic (43) effects. Recently, CNP has been shown to have protective effects against inflammatory and fibrotic reactions (44)(45). In vivo tests have revealed that CNP attenuates acute lipopolysaccharid-induced lung lesions (LPS) (46). CNP also regulates the secretion of inflammatory cytokines (47)(48).

In the inflammatory phase, expression levels of various chemokines, cytokines and growth factors are high and these mediators exert their profibrotic activity through the activation and proliferation of fibroblasts (49). Considering the pathophysiological importance of fibroblast activation in pulmonary fibrosis (50), and the above mentioned biological effects, it is suggested that there is a direct effect on pulmonary fibroblasts by natriuretic peptides. These insights suggest the use of therapeutic agents that increase the concentration of these peptides in the more severe stages of COVID-19 infection when a fibrotic pulmonary state is present. In association with evidence of antifibrotic and antihyperproliferative effects, the studies also show direct antiffiammatory effects mediated by the action of natriuretic peptides. In particular, some studies associate

the BNP peptide with an important inhibitory effect on NALP3 inflammasome activation, which is related to BNP-induced downregulation of NF-kB and ERK1/2 activation. The data indicate a powerful anti-inflammatory and immunomodulatory role for this peptide. (51) These effects mediated by natriuretic peptides suggest an important role in COVID-19 infection.

NT-proBNP in patients with severe COVID-19

BNP is synthesized as a prehormone (proBNP), upon release into the bloodstream it is divided into equal proportions in biologically active BNP and biologically inactive NT-proBNP.

Stress and myocardial damage are the main release stimuli for BNP and NT-proBNP, studies have shown that increased cytokines and an inflammatory state are important additional factors that induce hormone secretion. (52) BNP is degraded by plasma through endopeptidase Neprylisin (NEP), NT-proBNP is excreted mainly by renal excretion. BNP and NT-proBNP are important biomarkers for the evaluation of cardiac function. As described above, cardiac lesions are a common condition among patients hospitalized with COVID-19. In fact, one study indicates that 19.7% of patients out of a total of 416 cases with COVID-19 suffered cardiac damage with more unfavorable clinical outcomes than those without cardiac damage (53). Another recent study showed that the NT-proBNP marker increased significantly in more severe cases of COVID-19 (54) suggesting a relationship between high plasma levels of NT-proBNP, heart damage and risk of death in patients with severe COVID-19. The explanation for the increase in NT-proBNP in severe COVID-19 is probably due to cardiac complications resulting from up-regulation of the sympathetic and angiotensin renin (RAS) system, cytokinic cascade and systemic inflammation. In particular, cytokine storm (55)(56) could probably play an important role in cardiac damage (57). In addition, overactivation of RAS with reduced ACE-2 concentration, as evidenced in the more severe stages of COVID-19 infection, may lead to increased synthesis of Ang II with pro-inflammatory and profibrotic effects (mediated by AT-1 receptors) which facilitates the secretion of NT-proBNP (58)(59). Pending well-structured and in-depth studies, to assess whether the NT-proBNP marker can be a useful diagnostic test to assess the severity of COVID-19 infection, all the considerations expressed suggest a therapeutic drug solution with the action of increasing the concentration of natriuretic peptides in circulation, decrease the concentration of NT-proBNP, increase the RAS axis via ACE-2 with increased synthesis of Ang 1-7 and Ang 1-9 with antifibrotic and

anti-inflammatory effects, and decrease the effects of Ang II on the AT-1 receptor (60)(61)(62) (63)

Potential role of Sacubitril/valsartan

Sacubitril/valsartan is the first of a new class of drugs with a therapeutic indication for the treatment of chronic symptomatic heart failure with reduced ejection fraction. Sacubitril is a neprilisin inhibitor (NEPi), valsartan an angiotensin II receptor antagonist (ARBs) (64). Based on the considerations described above, the association sacubitril/valsartan could be an important therapeutic solution to combat COVID-19 infection. The use of the sacubitril/valsartan association could be of clinical benefit for several reasons, in particular the antagonism on the AT-1 receptor mediated by valsartan would lead to increased receptor occupation by the Ang II of the AT-2 receptor with antifibrotic, antiflammatory, antihyperproliferative and vasodilating effects with potential benefits on both pulmonary lesions caused by fibrotic tissue and cardiac damage caused by COVID-19. In addition, the actions of Ang-II on the AT-1 receptor, which mediates vasoconstriction, profibrotic and hyperproliferative effects, are blocked. Finally

Angiotensin II can cause increased inflammation through production of IL-6, TNF-α and other inflammatory cytokines mediated by AT-1. (65)(66)(67) It is known that in the more severe stages of COVID-19 infection there is a decrease in ACE-2 which plays a protective role. In fact, ACE-2 synthesizes Ang 1-7 and Ang 1-9 with known anti-inflammatory, vasodilating, antifibrotic and antihyperproliferative effects. (68)(69) The antagonism on AT-1 receptors leads to a compensatory increase of ACE-2. (70) Finally, after ARBs administration the response to hypertrophic growth induced by TNF-a is significantly attenuated (71) (Figure 1).

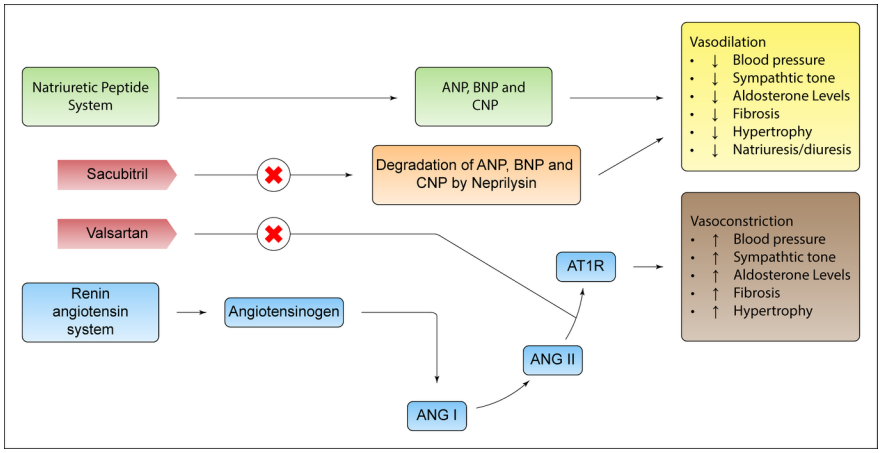

Figure 1 : *Sacubitril/Valsartan mechanism of action and biological effects*

The beneficial effects of NEPi are attributable to decreased degradation of natriuretic peptides. Natriuretic peptides cause vasodilation by stimulating the guanylate cyclase receptor to produce cGMP. In addition, sacubitril administration is known to decrease NT-proBNP, which in severe cases COVID-19 is increased. In patients with COVID-19, with and without symptoms attributable to pneumonia, there is evidence of a significant increase in NT-proBNP, regardless of left ventricular dysfunction. Indeed, studies show that NT-proBNP levels are also the results of acute renal lesions and pro-inflammatory molecules such as interleukin-1 and C-reactive protein,(72) In addition, natriuretic peptides act to suppress the renin-angiotensin and sympathetic systems and decrease endothelin secretion. In addition, as mentioned above, natriuretic peptides also exert anti-inflammatory, antifibrotic and antihypertrophic effects. In particular, some evidence shows direct mediated anti-inflammatory effects. In particular, some studies associate the BNP peptide with an important inhibitory effect on the activation of inflammatory NALP3, which is related to the reduction of BNP-induced NF-kB and ERK1/2 activation. In addition, for this class of drugs acting on RAS, there is potential indirect protection against SARS-CoV-2. In fact, patients with cardiovascular disease are at high risk of pneumonia, studies show that the use of drugs that block RAS decreases this risk. (73)(74) On the basis of the evidence described and in relation to the hypotheses suggested by us, the use of the sacubityl/valsartan association in patients with COVID-19, especially in severe cases, could be of therapeutic benefit, with cardioprotective, anti-inflammatory and antifibrotic effects capable of fighting lung damage, through an increase in the natriuretic peptide system and a decrease in the effects of AT-1 receptor-mediated Ang-II. Well-structured clinical studies are required to confirm these hypotheses.

Conflicts of interest

None of the Authors have conflicts of interest to disclose.

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None

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The authors certify that the manuscript is original, never submitted to other journal for publication before. All authors contributed equally to the manuscript and had the opportunity to revise and approve the final text.

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Dr. A.Vitiello has nothing to disclose

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