Julio, 2021 J App Mol Cell Bio. Vol. 8:*p* 1-5
http://dx.doi.org/10.21065/24122580.8.1

CONSORTIUM

Editorial Article

THE CARDIOVASCULAR DISTRESS TRIGGERED BY SARS-COV-2 MIGHT HELP TO SHAPE AN ULTIMATE FATAL IMMUNE INSULT WHICH NECESSARILY REQUIRES A MULTI-DISCIPLINARY THERAPEUTIC APPROACH.

Julio L. Padron Velazquez.

Studio Eutropi, Via Pompei 46, Ardea 00040, Rome Italy.

History:
Received: January 10, 2021
Accepted: February 19, 2021
Published: February 21, 2021
Collection year: 2021
Status: Published

Identifiers and Pagination:
Year: 2021
Volume: 8
First Page: 1
Last Page: 5
Publisher ID: 24122580.8.1
DOI:
http://dx.doi.org/10.21065/24122580.8.1

Corresponding author:
Julio Lazaro Padron Velazquez PhD
Via Pompei, 46, Ardea 00040 (RM).
Via Monopoli 33E, Roma 00133, Italia
Ricapiti Telf: Cell: +39-333-4714633
E-mail: jl.padron.v@gmail.com

Citation:
Juloi L. pardon Valazquez. The cardiovascular distress triggered by SARS-COV-2 might help to shape an ultimate fatal immune insult which necessarily requires a multi-disciplinary therapeutic approach. J App Mol Cell Bio.2021;8: *p* 1-6

The corona virus SARS-CoV-2 is the etiologic agent of the current pandemic outbreak of COVID-19 that is afflicting humankind through the whole globe since December of 2019 [1]. Huge efforts and resources are focused on many aspects of COVID-19 pathology and therapy, and indeed important advancements have been obtained in a relative short period of time. Following modest success with several intuitive and empirical therapeutic approaches (antiviral, antibiotics, anticoagulant, cortisone, immunosuppressive, cytokines) [2] most hopes are currently paying attention to a number immune based therapeutics such as several vaccines already entered in large clinical use [3].

However, though some important insights are also emerging on basic studies addressing SARS-CoV-2 pathogenic mechanisms of action, much have yet to be done in this regard to fully understand SARS-CoV-2 pathogenic processes and therefore implement the most appropriate therapeutic strategies. The extreme complexity of the pathological outcome observed on COVID-19 cannot be successfully solved with palliative therapies by simply using empiric or intuitive approaches. A really rational therapeutic intervention necessarily requires a multidisciplinary strategy with a deep knowledge of all mechanisms involved, and what is more, it might not be even enough to simply know all mechanisms, but also the precise algorithm or time line with which such events take place. It won't be unexpected to realize that a potentially valuable therapeutic tool given at the wrong time might result into an ineffective outcome or even worse; into deleterious consequences.

In this regard it might worth to dedicate widen efforts to better understand the extent by which SARS-CoV-2 might be triggering a cardiovascular misbalance as a primary strategy to escape from an appropriate immune response thus leading to ultimate fatal immune insult.

One of the first and most important steps on any viral infective pathway include the binding of the viral envelop to their specific target cell in order to subsequently initiate fusion, entrance and replication mechanisms. It is widely well accepted that entering of SARS-CoV-2 to pulmonary cells is mediated by the specific binding of the spike protein (S), present on the surface of the viral capsid, to the angiotensin II converting enzyme type 2 proteins (ACE2) anchored on the surface of target pulmonary cells [4]. At this point a first question to reflect on could be whether the "choice" of ACE2 was simply casual, being any surface molecule on pulmonary cells a valuable target, or whether there might be some other specific "logic" in favor of the SARS-CoV-2 pathogenic mode of action and immune escape strategy. To this purpose, it would be reasonable to go deeper into the comprehension of AT-II function and homeostasis and how that is impaired by spike protein biding to ACE2.

Being aware of the role of ACE2 on AT-II catabolism [5], at first sight it won't be irrational to anticipate that the occupancy of ACE2 by Spike might result into a surplus on AT-II [6] which could be then additionally exacerbated following inhibition on ACE2 expression upon SARS-CoV-2 cell entrance and replication [7]. Noticeably, whereas normal levels of AT-II ensure a

Funding:
The authors received no direct funding for this research.

Competing Interests:
The authors declare no competing interests

Additional information is available at the end of the article.

physiological degree of vasoconstriction, on the other hand it is well known that AT1R overstimulation, due to an eventual AT-II excess, might result not only into an increased vasoconstriction leading to hypertension [8] but also to the activation of several mechanisms leading to oxidative stress, vascular dysfunction and inflammation [9] which could ultimately drive into some of the pathogenic events observed on COVID-19 disease progression such as increased thrombogenesis, platelet aggregation and inflammatory cell adhesion to endothelial cells [10].

In this manner, meanwhile cardiovascular system goes in letdown SARS-CoV-2 challenge might gain important timing advantages to extend viral invasion (applying if necessary to some ACE2 independent entrance mechanism as for example Slavic Acid Residues [11]). However, the possibility of rescuing at this stage cardiovascular and whole organism homeostasis might be not yet fully defeated. Indeed, an alternative mechanism of negative feedback aimed at counteracting the AT-II excess is expected to enter in action. Once AT-II catabolism has been seriously dismissed a second approach in order to avoid further AT-II accumulation would be blocking AT-II anabolism.

It is well known that AT-II is produced following angiotensin I (AT-I) catabolism by the action of an enzyme called angiotensin I converting enzyme type 1 (ACE) [12] which is negatively down-regulated by high levels of AT-II [13]. At this point it would be rational to expect that inhibition of ACE by high levels of AT-II might finally avoid any further accumulation of AT-II.

Though indeed it might seems a good compensatory mechanism it worth remembering that the already produced amount of AT-II could be still over stimulating AT1R therefore still leading to such pathogenic events mentioned above. Moreover, what is more worrying; ACE is also the key enzyme in the catabolism of another important player on cardiovascular homeostasis: bradykinin (BK) [14]. In other words, whereas ACE inhibition might effectively avoid any further AT-II accumulation, on the other hand unfortunately ACE inhibition might also result into an abnormal accumulation of BK, which could explain some other pathogenic events observed on COVID-2 disease such as hypotension, dry cough, bronchospasm and edema [15].

Noticeably, these events are closely resembling some adverse side effects observed in certain patients under therapy with ARBs and/or ACE inhibitor (ACEI) (i.e. increased susceptibility to infections, upper respiratory distress, caught, asthma and sepsis) [16]. In fact, a careful analysis of the precise timeline of COVID-19 pathogenic events might help to understand some apparent contradictory reports regarding the opportunity of suspending, continuing or implementing therapies with ARBs, ACEI[17] as well as some other pharmacological agents such as recombinant human ACE2 (rhACE2) [18]. Whereas at certain time point some of these drugs might provide some benefit, at another time point it might be deleterious.

Moreover, just to further set hurdles the reasoning, it is striking to notice that the expression of some of these major players on keeping homeostasis as for example ACE2 (thus plausibly susceptibility to SARS-CoV-2) varies with age, ethnicity, smoking, gender and polluted environment among other factors [19]. In the same manner, it worth also considering that pre-existing cardiovascular disorders and/or concomitant therapies might determine a different preliminary sensibility as well as a different reactive cardiovascular response to SARS-CoV-2 challenge [20]. In other words, a successful therapeutic approach to deal with COVID-19 cardiovascular complications might require a personalized analysis taking into account both intrinsic and extrinsic conditions of the subject as well as the precise timeline of the pathogenic processes happening.

Last but not least, it might be also relevant to consider that bystander cardiovascular and/or inflammatory altered conditions might determine a different pattern of immune response on different individuals leading therefore toward a protective or toward a susceptible immune profile [21]. Such analysis might be not only valuable to a better deal with patient immune specificity aimed at implementing a proper personalized immunotherapeutic approach, but also to develop more appropriate generalized immune therapeutic tools, such as vaccines, with an increased safety/efficiency profile.

Vaccines are certainly among the safer class of therapeutic tools humankind has ever develop, however it does not necessarily mean they are absolutely free of mild/severe side effects. Moreover, acceptable levels of efficacy is not easily granted, requiring in most of case many years to fully demonstrate proper protection which, in spite of large efforts and resources, in some case has not been reached yet (i.e. HIV). Noteworthy, the ability to raise long lasting large and/or broad levels of neutralizing antibodies (nabs) doesn't necessarily represent an effective protection. Actually in some case, as for example HIV, immune burden on producing nabs against gp120 (capsid surface protein designed for binding target cell) not only is not protective, but astonishingly it could represent a well-designed distraction mechanism aimed at deviating the attention and efforts of the immune system in order to favor a successful viral immune escape [22]. Likewise, it should not be underestimated the potential role of individual preexisting micro/macro immune-environmental conditions which, even in the presence of the same antigenic insult, could determine the development of either a right (protective) or a wrong (sensitizing) immune response [23].

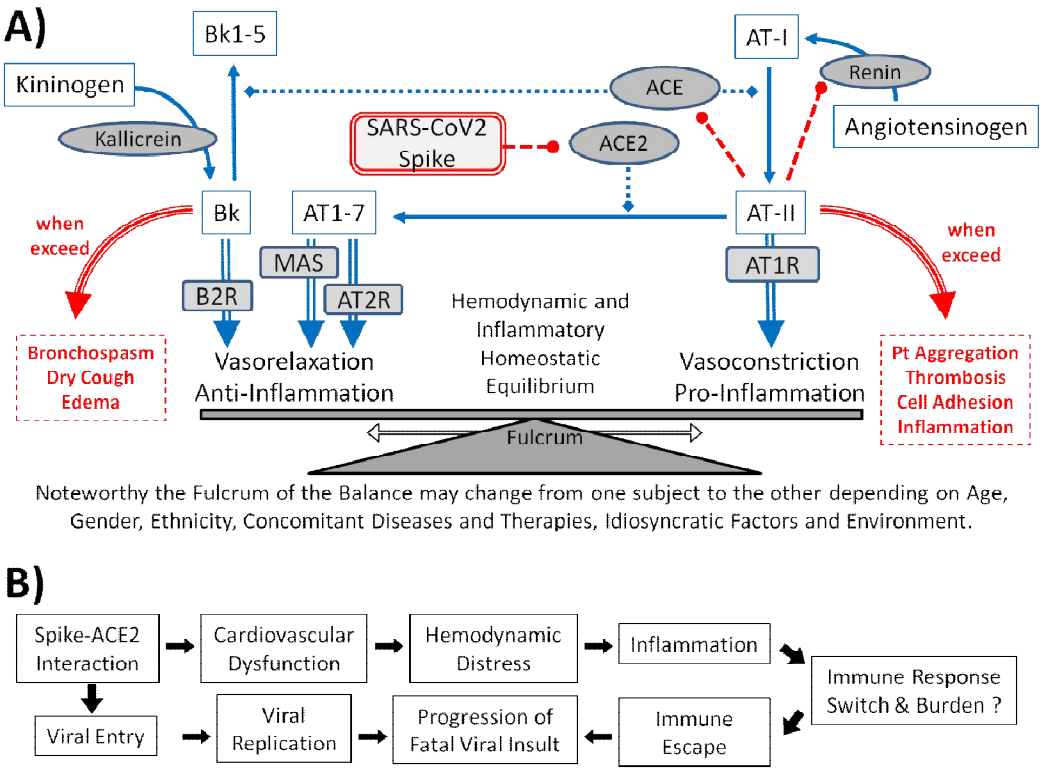

Figure 1. Oversimplified diagram illustrating major SARS-CoV-2 pathogenic mode of action.

In this regard, back to COVID-19 and trying to summarize, in our opinion it might be rational

to consider and to further explore in which extent the final fate of the immune insult caused by SARS-CoV-2, as well as the observed contradictory response to therapies, could be driven by the precise sequence of early events triggering a cardiovascular misbalance which could be more or less exacerbated in different subjects under different pre-established conditions.

Panel A) Spike protein from SARS-CoV-2, by inhibiting ACE2, causes a significant surplus on AT-II which in a first step conduces toward a pro-inflammatory status leading to hypertension, cell adhesion, platelet aggregation and thrombosis. At a second stage however it is plausible that such AT-II accumulation, due to the lack of AT-II catabolism, might inhibit ACE aiming to produce a negative feedback on its own anabolism while at the same time inhibiting the catabolism of a counterbalancing agent such as bradykinin. Though initially such action might indeed provide some compensatory mechanism, if persistent it might lead at the end to the occurrence of the other extreme adverse effects such as bronchospasm, dry cough and edema. Last but not least, it would be important to notice that such fragile hemodynamic and inflammatory homeostatic equilibrium is represented on a balance in which the fulcrum may vary from one subject to the other, determining therefore a more susceptible or a resistant profile.

Panel B) Early mechanism aimed at allowing viral entry mediates a parallel distress on the cardiovascular system resulting into an hemodynamic and inflammatory which later favor the occurrence of an inappropriate immune response which allow progression of the fatal viral insult.

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