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Effects of β-blockers on the sympathetic and cytokines storms in Covid-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a causative virus in the development of coronavirus disease 2019 (Covid-19) pandemic. Respiratory manifestations of SARS-CoV-2 infection such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) lead to hypoxia, oxidative stress, and sympatho-activation and in severe cases lead to sympathetic storm (SS). On the other hand, exaggerated immune response to the SARS-CoV-2 invasion may lead to uncontrolled release of pro-inflammatory cytokine development of cytokine storm (CS). In Covid-19, there are interactive interactions between CS and SS in development of multi-organ failure (MOF). Interestingly, cutting the bridge between CS and SS by anti-inflammatory and anti-adrenergic agents may mitigate complications that are induced by SARS-CoV-2 infection in severely affected Covid-19 patients. The potential mechanisms of SS in Covid-19 are through different pathways such as hypoxia, which activate central sympathetic center through carotid bodies chemosensory input and induced pro-inflammatory cytokines, which cross blood brain barrier and activate sympathetic center. β2-receptors signaling pathway play a crucial role in the production of pro-inflammatory cytokines, macrophage activation and B-cells for production of antibodies with inflammation exacerbation. β-blockers have anti-inflammatory effects through reduction release of pro-inflammatory cytokines with inhibition of NF-κB . In conclusion, β-blockers interrupt this interaction through inhibition of several mediators of CS and SS with prevention development of neural-cytokine loop in SARS-CoV-2 infection. Evidences from this study trigger an idea for future prospective studies to confirm the potential role of β-blockers in the management of Covid-19.

Keywords: SARS-CoV-2, cytokine storm, sympathetic storm

Background

It is well-known in the recent time that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a causative virus in the development of coronavirus disease 2019 (Covid-19) pandemic (1). This disease was initially documented in Wuhan province of China (2). The SARS-COV-2 virus is highly infective but about 15% of the patients require hospitalization and 5% may need intensive care (3). Approximately half of Covid-19 patients taken to intensive care units (ICU) die due to various complications (4). The severe COVID-19 complications include respiratory failure, cardiac arrhythmias, acute kidney injury, and stroke (5). Respiratory failure is a result of acute lung injury (ALI) and acute

respiratory distress syndrome (ARDS) (6). The respiratory system signs lead to hypoxia, oxidative stress, and sympatho-activation and in severe cases lead to sympathetic storm (SS)(7). SS is characterized by recurrent episodes of hyperhidrosis, hypertension, tachycardia, tachypnea, and hyperthermia (8).

On the other hand, exaggerated immune response to the SARS-CoV-2 invasion may lead to production of various inflammatory substances (9). There may be uncontrolled release of pro-inflammatory cytokine such as interleukins (IL-6, IL-1β, IL-8), tumor necrosis factor alpha (TNF-α) and chemokines that together lead to development of cytokine storm (CS) (10).

In Covid-19, there is interactive interaction between CS and SS in development of multi-organ failure (MOF) and life-threatening complications (11). However, cutting the bridge between CS and SS by anti-inflammatory and anti-adrenergic agents may mitigate complications that are induced by SARS-CoV-2 infection in severely affected Covid-19 patients (12).

Anti-adrenergic β-blockers are class of medications used in the management of cardiovascular disorders such as arrhythmia, acute coronary syndrome, and hypertension as well as other disorders like tremor and anxiety (13). β-blockers are either selective (block β1 or β2) or non-selective (block both β1 and β2). β-blockers reduce sympathetic stimulation-mediated by adrenalin and noradrenalin on β receptors (13). β1 receptors are located mainly on the heart and kidney while, β2 receptors are expressed primary in lungs, vascular smooth muscles, and gastrointestinal tract (14).

The objective of the present study was to elucidate the potential effects of β-blockers on both SS and CS in patients with severe Covid-19.

β-blockers and sympathetic storm in Covid-19

It has been reported that β-blockers such as propranolol, metoprolol, and labetalol are effective in the management of SS by mitigation of autonomic dysregulation and

sympathetic spells in patients with thalamic injury (15). SS is due to increased activity of sympathetic nervous system (SNS) at the expense of the parasympathetic nervous system (PSNS) due to brain injury (16). The severity of traumatic brain injury (TBI) correlates with the level of sympathetic activation. The implication is that early use of β-blockers in TBI may attenuate development of SS (17). Luostarinen *et al.*, retrospective study showed that TBI in Covid-19 patients did not affect disease severity (18). About 55% of hospitalized Covid-19 patients develop neurological signs (19). These signs may remain for about three months following SARS-CoV-2 infection, suggesting development of latent brain injury (20).

Invasion of central nervous system (CNS) by SARS-CoV-2 has remained speculative (21). However brain injury in Covid-19 patients might be due to direct effect of SARS-CoV-2. COVID-19 may lead to brain injury because it manifests with hypoxemia, autoimmune response, thrombosis and CS (22). Notably, involvement of peripheral nervous system (PNS) and autonomic nervous system (ANS) results in an imbalance between SNS and PSNS with development of SS (23). The imbalance of SNS/PSNS axis of ANS may affect release of pro-inflammatory cytokines and immune-inflammatory response during course of Covid-19 (24). In this context, high circulating catecholamine levels may reflect sympathetic-mediated neutrophilia and T cell dysfunction in Covid-19 due to SS (25). Thus, development SS in Covid-19 is through central and peripheral effects SARS-CoV-2 that increase sympathetic outflow [**Figure 1**].

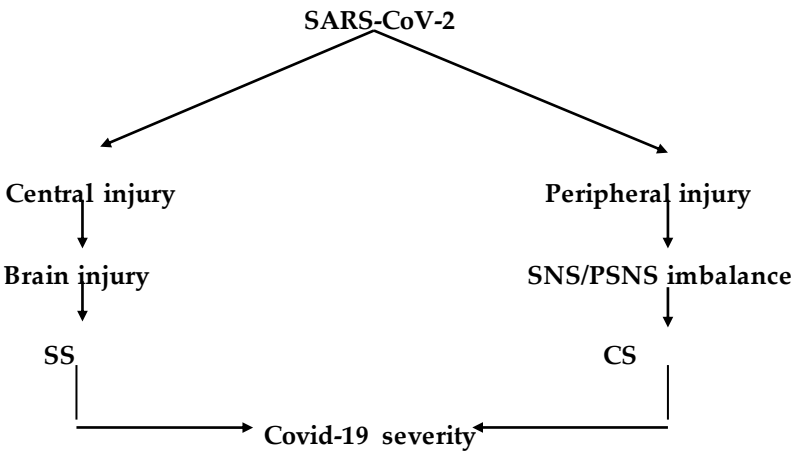


Figure 1. **SARS-CoV-2 infection and development of sympathetic and cytokine storms:** Central effect of SARS-CoV-2 leads to brain injury and development of sympathetic storm (SS). Peripheral effect of SARS-CoV-2 leads to induction imbalance between sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) and development of cytokine storm (CS). Both of SS and CS lead to Covid-19 severity.

The potential mechanisms of SS in Covid-19 are through the three pathways including; ALI/ARDS-induced hypoxia activate central sympathetic center through carotid bodies chemosensory input (26). SARS-CoV-2-induced neuroinflammation directly activate sympathetic centers like locus coeruleus (LC), rostral ventrolateral medulla (RVLM) and hypothalamic paraventricular nucleus (HPVN) (27). SARS-CoV-2-induced pro-inflammatory cytokines, which cross blood brain barrier and activate sympathetic center [**Figure 2**] (28).

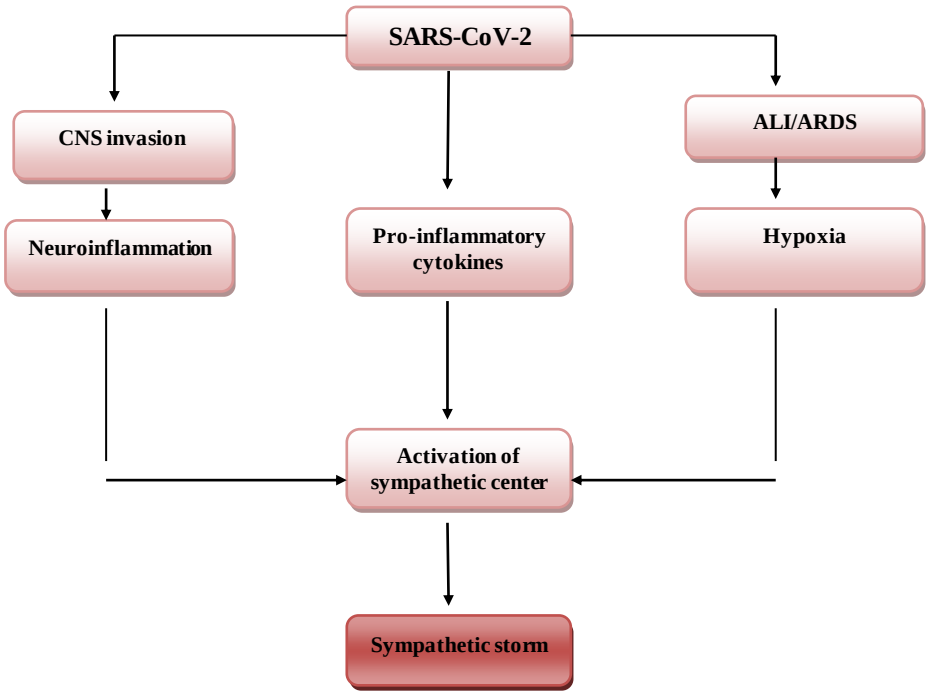


Figure 2. SARS-CoV-2-induced sympathetic storm. SARS-CoV-2 acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)-induced hypoxia, SARS-CoV-2-induced neuroinflammation and release of pro-inflammatory cytokines activate central sympathetic center with development of sympathetic storm.

Moreover comorbidities that induce a high sympathetic activity such as diabetes mellitus and hypertension may exacerbate the cardiac arrhythmia, cardiac arrest and acute myocardial infarction (29). Development of Covid-19 severity is linked with SS and vagal suppression that culminate into the CS (30). It is thus suggested that vagal stimulation might be valuable in Covid-19 patients through modulation of SS and release of pro-inflammatory cytokines (31). It has been shown that cholinergic agonists inhibit inflammation via suppression of inflammatory signals such as high mobility group protein 1 (HMGB1) (32). Furthermore, molecular docking study observed that nicotinic acetylcholine receptor (nAChR) may be a potential binding receptor for SARS-CoV-2(32). Inhibition of nAChR by SARS-CoV-2 lead to inhibition of PSNS and exaggeration of SNS with subsequent progression of CS due to inhibition of vagal anti-inflammatory mediated by diminution of nAChR activity (33). Likewise, α-1 and β-receptor antagonists have valuable effects in Covid-19 via lessening of SS and development of CS (34). For that reason, β-blockers reduce sympathetic stimulation and inhibit the interaction between SARS-CoV-2 and receptor binding sites of angiotensin converting enzyme 2 (ACE2) and CD147 (35) [**Figure 3**].

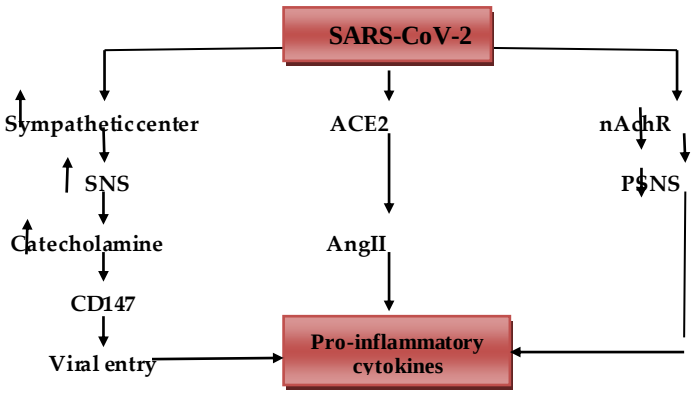


Figure 3. SARS-CoV-2 and release of pro-inflammatory cytokines: SARS-CoV-2 activates sympathetic center, increase activity of sympathetic nervous system (SNS), release of catecholamine, which activate expression of CD147 that increase viral entry. SARS-CoV-2 downregulates ACE2 that increase circulating angiotensin II (AngII). SARS-CoV-2 inhibits anti-inflammatory nicotinic acetylcholine receptor (nAChR) with reduction activity of parasympathetic nervous system (PSNS). These changes together trigger release of pro-inflammatory cytokines.

β-blockers reduce SS-induced cardiac arrhythmia, and destabilization of coronary plaques due to high circulating catecholamine, which cause positive inotropic and chronotropic effects through β1 receptor (36). As well, β-blockers reduce cardiac injury caused by sympathetic over-activation. Cardiomyocyte inflammation results from induction of local TNF-α and IL-6 expression (37).

Moreover, binding of SARS-CoV-2 to the ACE2 leads to deregulation of renin-angiotensin system (RAS) with upregulation of vasoconstrictor angiotensin II (AngII). There is a co-current down-regulation of vasodilator Ang 1-7 leading to hypertension, sympathetic stimulation and development of ALI and ARDS (38). β-blockers therefore reduce the activity of RAS though inhibiting release of renin from renal juxtaglomerular cells, and so protect the lungs and heart from exaggerated RAS and SS (39). Experimental study by Danukalo *et al.*, illustrated that AngII increases firing and activity of LC with propagation of sympathetic activation and hypertension in rats (40). Besides, β-blockers like propranolol modulate the activity and sensitivity of LC and prevent sympathetic stimulation in patients with migraines (41). Indeed, non-selective and lipophilic β-blockers like propranolol have potent effect in suppression of catecholamine from presynaptic adrenergic neurons through inhibition of excitatory presynaptic β2 autoreceptor (42). Taken together, β-blockers reduce development of SS directly or indirectly through suppression of central effect of AngII.

β-blockers prevent SS-induced ALI as high circulating catecholamines are linked with development of ALI/ARDS (43). In addition, β-blockers prevent ALI through modulation of neutrophilia, lymphopenia, and release of pro-inflammatory cytokines (44). In a retrospective study that involved 651 patients in ICU with sepsis, the patients on chronic β-blockers therapy had lower risk of sepsis-induced ARDS. The patients required less

mechanical ventilation due to upregulation of protective alveolar β2 adrenoceptors (45). Likewise in a randomized controlled clinical trial of 314 patients with acute respiratory failure in the ICU showed that patient on β-blockers therapy had lower in hospital mortality rate (46). Contrastingly, Mutlu *et al.,* observed that β2-agonists improve alveolar fluid clearance in patients with pulmonary edema through up-regulation of alveolar epithelial sodium active transport (47). In a study that involved 79 patients with ALI is associated with impairment of pulmonary alveolar clearance rate (48). These findings imply that selective β1-blockers are safer than non-selective ones in preventing attenuation of β2 adrenoceptors beneficial effect.

The findings support the favorable effects of β-blockers in the mitigation of SS-induced ALI/ARDS in severely affected Covid-19 patients [**Figure 4**].

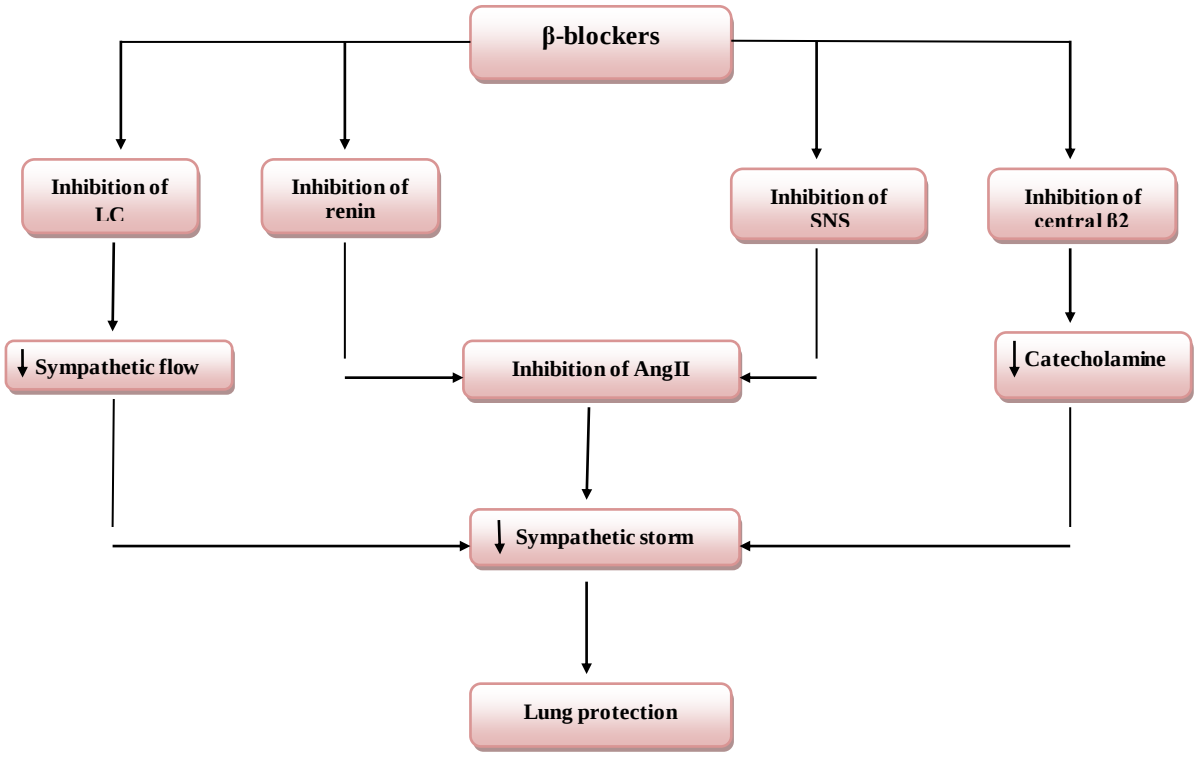


Figure 4. Role of β-blockers in lung protection: β-blockers inhibit sympathetic nervous system (SNS), renin release, locus coeruleus (LC) activity, and central presynaptic β2 receptors that decrease release of catecholamine and angiotensin II (AngII) with subsequent inhibition of sympathetic storm and lung protection.

β-blockers and cytokine storm in Covid-19

CS or cytokine releasing syndrome is a systemic inflammatory syndrome characterized by high circulating pro-inflammatory cytokines. CS also involves abnormal immunological hyperactivation as that are provoked by pathogens, autoimmune reactions and cancers (49). In Covid-19 pro-inflammatory cytokines including IL-6, TNF-α, IL-1β, and macrophage inflammatory protein (MIP) are elevated. Plasmablasts, CD4 and CD8 and other immune cells are also activated in CS (50). The interaction between SARS-CoV-2 and ACE2 on the affected cells induce cells damage. The interaction also cause release of damage and inflammatory signals. The mentioned signals activate macrophages for release of chemokines and pro-inflammatory cytokines that trigger T cells recruitment and activation (51). In addition, SARS-CoV-2 spike protein can activate CD147 and toll like receptor 4 (TLR4) leading to stimulation of myeloid differentiation 88(MyD88) pathway. Myeloid differentiation provokes nuclear factor kappa B (NF-κB), which stimulate release of pro-inflammatory cytokines and development of CS (52) [**Figure 5**].

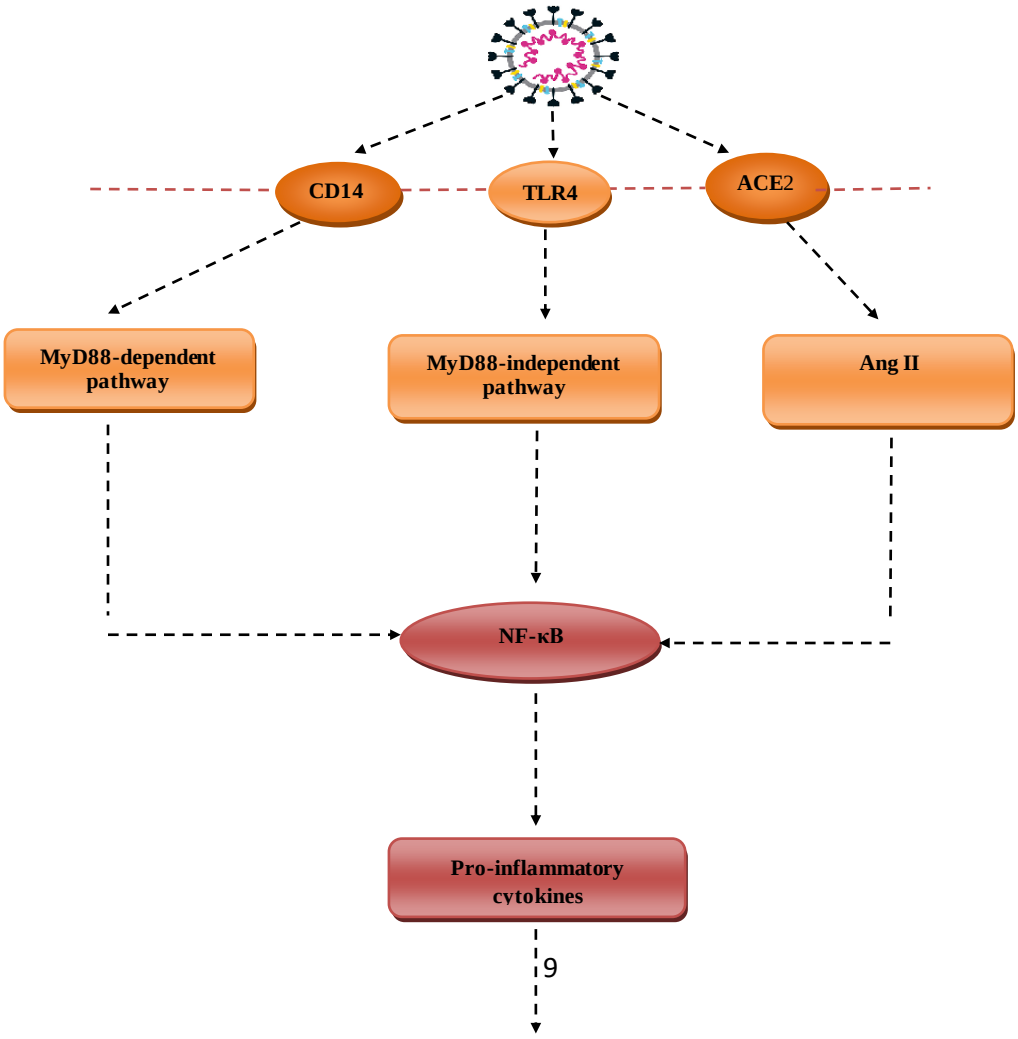


Figure 5. Role of SARS-CoV-2 in the development of cytokine storm (CS): SARS-CoV-2 through activation of CD147 activate myeloid differentiation 88 (MyD88), through toll-like recptor 4 (TLR4) and through ACE2 activate angiotensin II (AngII) that together trigger NF-κB pathway, which stimulate release of pro-inflammatory pathway and development of cytokine storm.

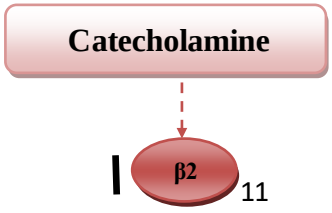
Interestingly, adrenergic receptors are linked with immunological disorders and development of immune-mediated ALI since 90% of β-receptors are located in the lung alveoli with β2 predominant in 70% (53). β2 receptors are expressed by all immune cells especially macrophages ,dendritic cells and lymphocytes (54). Therefore, β2-receptors signaling pathway play a crucial role in the production of pro-inflammatory cytokines, macrophage activation and B-cells. The B-cells are involved in the production of antibodies which exacerbates the inflammation (55). Thus, β2-agonists may induce alveolar inflammation and pulmonary microvascular thrombosis via accelerated release of IL-6 (56). Nossent *et al.,* observed that β2-agonists increase risk of venous thrombosis through activation of von Willebrand factor and factor VIII (57). In addition, activation of β2 receptors leads to generation of reactive oxygen species (ROS) and induction of oxidative stress. Oxidative stress activates the release of IL-6, promotion of Th2 immune response and inhibition of interferon gamma (INF-γ) (58).

β-blockers have anti-inflammatory effects through reduction release of IL-6 and TNF-α, with inhibition of NF-κB and signal transduction and activator of transcription 3 (STAT3)(59). These pro-inflammatory cytokines and inflammatory signaling pathways are highly activated in Covid-19 in the progression of CS (60). Therefore, β-blockers may attenuate development of CS in patients with severe Covid-19 (61). Additionally, β-blockers may reduce SARS-CoV-2-induced coagulopathy and pro-thrombotic complications through inhibition of platelet aggregations and factor VIII (62). β-blockers alleviate endothelial

dysfunction and microvascular dysfunction linked with coagulopathy in Covid-19 through suppression of vascular endothelial growth factor (63).

CS is also developed due to activation of nod-like receptor pyrin 3 (NLRP3) inflammasome by SARS-CoV-2 viroporin (64). Gao *et al.*, found that β-blocker nebivolol inhibits NLRP3 inflammasome in obesity-induced vascular remodeling in experimental animals (65). So, β-blockers could have potential benefit in mitigating progression of SARS-CoV-2-mediated CS. SS with high catecholamine levels activate RAS with induction of AngII-mediated ALI and release of pro-inflammatory cytokines. Therefore β-blockers through inhibition of renin release and suppression of RAS may weaken release of pro-inflammatory cytokines and development of CS (66). Furthermore, macrophage activation syndrome (MAS) like disease is developed in severely affected Covid-19 leading to ALI, ARDS, and MOF (67). Xia *et al.*, illustrated that high circulating catecholamine levels are associated with macrophages activation and release of pro-inflammatory cytokines (68). A prospective study involving 32 patients with immune mediated dilated cardiomyopathy showed that β-blockers therapy reduces pro-inflammatory TNF-α. β-blockers increase anti-inflammatory IL-10 through inhibition of macrophage activation (69). Thus, β-blockers may reduce development of MAS through inhibition of macrophage activation and release of pro-inflammatory cytokines (70). Nateasan preprinted study summarized the beneficial effects of β-blockers in Covid-19 in some points including that β-blockers improve oxygenation, reduce bronchial secretion, inhibit entry of SARS-CoV-2 through ACE2 and CD147, inhibit release of pro-inflammatory cytokines, reduce development of pulmonary edema and ARDS, inhibit development of endothelial dysfunction and coagulopathy, block proliferation of SARS-CoV-2, and finally suppression of NLRP3 inflammasome and NF-κB signaling (62).

Taken together, according to these findings, β-blockers might have potential therapeutic modality in prevention development of CS in Covid-19[**Figure 6**].



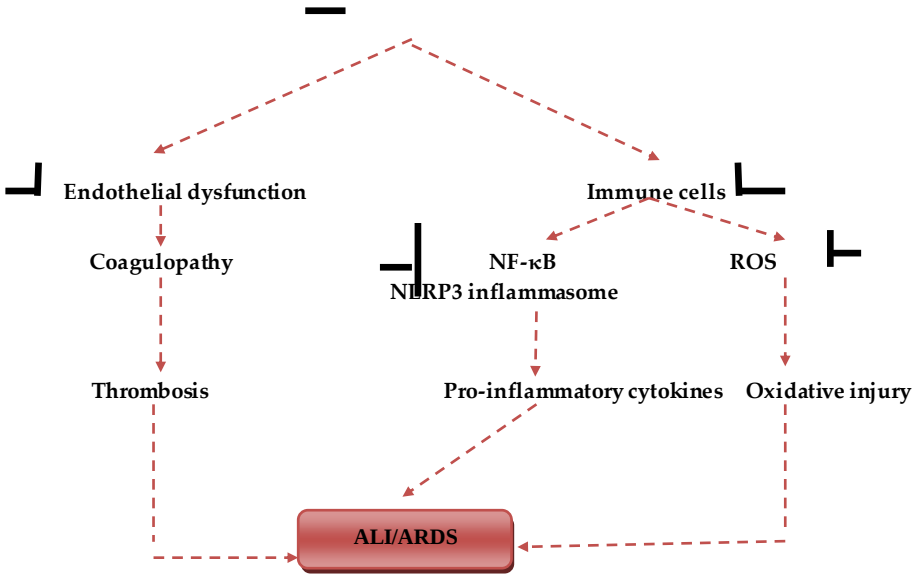


Figure 6. Catecholamine and acute lung injury: catecholamine during SARS-CoV-2-induced sympathetic storm , activate β1, which activate NF-κB and NLRP3 inflammasome of immune cells macrophages and neutrophils induces release of pro-inflammatory cytokines. Activation of immune cells trigger generation of reactive oxygen species (ROS).activation of β2 leads to development of endothelial dysfunction, coagulopathy and thrombosis. Together these changes cause acute lung injury (ALI) and acute respiratory syndrome (ARDS).

Crosstalk between sympathetic and cytokine storms in Covid-19

It is proposed that cortical inhibitory GABAerigic neurons inhibit pre-sympathetic hypothalamic PVN neurons (71). These GABAerigic neurons have high expression of ACE2 receptors. Therefore down-regulation of ACE2 receptors during SARS-CoV-2 infection may suppress these inhibitory interneurons with activation of hypothalamic PVN sympathetic neurons (72). Down-regulation of ACE2 during SARS-CoV-2 infection also augments AngII level, which has potent stimulatory effect on the central hypothalamic PVN sympathetic neurons (73). Notably, central sympathetic stimulation due to SARS-CoV-2 infection increases circulating catecholamine. Catecholamines activates macrophages and neutrophils for release of pro-inflammatory cytokines. Activated macrophages and neutrophils also release catecholamine, which act in a paracrine manner for augmentated release of pro-inflammatory cytokines (74). Rlddell speculated that catecholamine acts as a fuel for activation and boosting of macrophages and neutrophils and development of CS (75).

Indeed, high catecholamine levels interact with pro-inflammatory cytokines in progression of capillary leak syndrome and development of MOF (76). These findings confirm the potential nexus between SS and CS in the development of MOF in patients with severe Covid-19(77). Experimental study showed that interruption of catecholamine synthesis and release by metyrosine inhibits development of CS in mice induced by T cell targeting antibodies (78).

Furthermore, high catecholamine levels during development of SS in Covid-19 patients facilitate entry of SARS-CoV-2 via induction expression of CD147. Expressed CD147 causes damage of lung alveolar basement membrane through activation of matrix metalloproteinase (MMPs) (79). In turn, alveolar membrane injury triggers release of catecholamine from activated macrophages and neutrophils with generation of vicious cycle of injury (80). Thus, inhibition of CD147 may alleviate ALI through disruption of catecholamine-mediated acute inflammatory reactions (81). Hence, β-blockers may reduce pulmonary inflammation and alveolar dysfunction through inhibition of CD147 and MMPs in SARS-CoV-2 infection (82). Inhibition of CD147 leads to significant down-regulation of NF-κB signaling, which is the central pathway for activation release of pro-inflammatory cytokines (83). Therefore, β-blockers through inhibition of CD147, NF-κB signaling and other inflammatory molecules (84) are potentially considered as anti-inflammatory agents and may mitigate Covid-19 severity.

It has also been proposed that α1-blockers like prazosin are effective in mitigation of CS in Covid-19 through inhibition release of IL-6 (85). Therefore, dual β and α1-blocker like labetalol might be more effective in suppression development of CS through complete blocking of catecholamine effects on the immune cells during SS in Covid-19 (86).

Interestingly, β-blockers mainly carvedilol has anti-oxidant effects that are induced by high catecholamine level in patients with heart failure (87). Therefore, β-blockers block development of oxidative stress during development of SS and CS in Covid-19 that is associated with various complications like endothelial dysfunction and coagulopathy (88).

It has been shown that toxic gas-induced pulmonary alveolar membrane injury trigger cascades for development of oxidative stress. Oxidative stress then provokes neutrophils and macrophages to release pro-inflammatory cytokines and development of ALI (89). Similarly, oxidative stress injury in SARS-CoV-2 infection escalates release of pro-inflammatory cytokines in oxidative-dependent manner in the development of CS (90).

Notably, myeoloperoxidase (MPO) is regarded as a linking marker between oxidative stress and inflammation. High MPO activity is linked with development of cardiovascular complications (91). MPO is regarded as a natural immune response, which release hypochloruous acid (HOCI). HOCL competes for oxygen binding at heme molecule of hemoglobin causing heme destruction and release of free iron that cause acute tissue injury through generation of ROS in Covid-19 (92). These verdicts confirm that MPO-indued oxidative stress is regarded as chief central pathway linking development of CS and SS in Covid19. β-blockers mostly metoprolol block the activity of MPO and mitigate development of oxidative stress and further development of sympoatho-cytokine storm (93). Therefore, there is considerable crosstalk between SS and CS in Covid-19 [**Figure 7**].

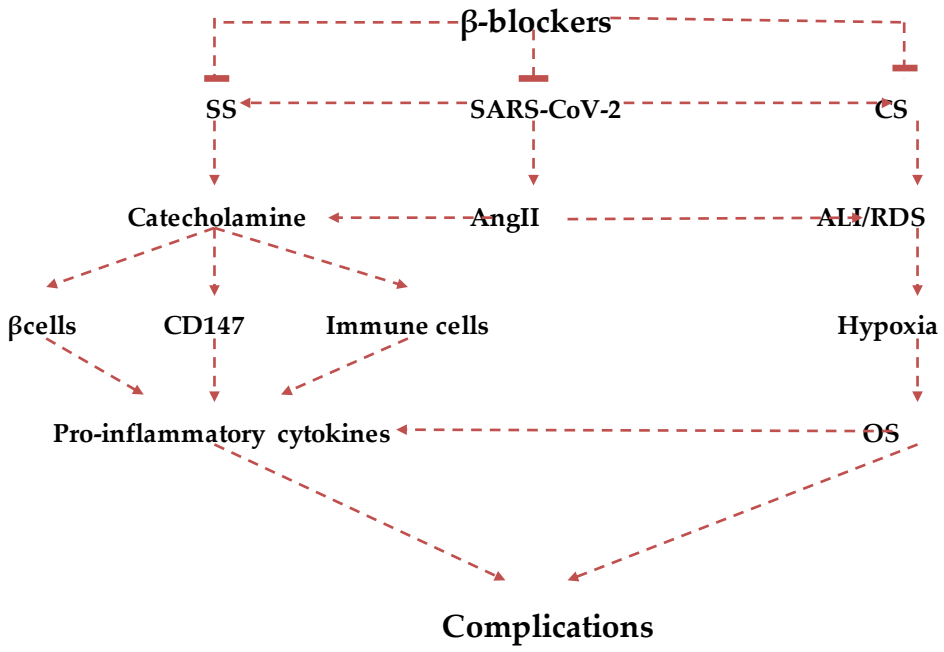


Figure 7. Role of β-blockers in the irruptions the crosstalk between cytokine (CS) and sympathetic storms(SS): β-blockers block reduces release of catecholamine and decrease its stimulatory effect on β2, CD147 and immune cells with reduction release of pro-inflammatory cytokines. The anti-

inflammatory effects of β-blockers also attenuate CS-induced acute lung injury (ALI) and acute respiratory syndrome (ARDS), development of oxidative stress (OS) and final systemic complications.

β-blockers are effective mitigators of both SS and CS through interruption of catecholamine-β receptors interaction and inhibition release of pro-inflammatory cytokine and development of CS in Covid-19.

CONCLUSION

Anti-inflammatory effect of β-blockers through inhibition release of pro-inflammatory cytokines contributes into mitigation of CS progression. As well, β-blockers attenuate development of SS due to SARS-CoV-2 infection-induced catecholamine release and sympatho-excitation. CS and SS interact at various levels to cause lethal complications in patients with severe COVID-19 like ALI, ARDS and MOF. However, β-blockers interrupt this interaction through inhibition of several mediators of CS and SS. β-blockers also prevents development of neural-cytokine loop in SARS-CoV-2 infection. Evidences from this study trigger an idea for future prospective studies to confirm the potential role of β-blockers in the management of Covid-19.

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