

# Cardiac complications in patients with COVID-19 infection

Vladimir Mitov<sup>1</sup>, Aleksandar Jolić<sup>1</sup>, Dragana Adamović<sup>1</sup>, Milan Nikolić<sup>1</sup>, Marko Dimitrijević<sup>1</sup>, Tomislav Kostić<sup>2</sup>, Milan A. Nedeljković<sup>3</sup>

<sup>1</sup>Department for invasive cardiology, Medical centre Zaječar, <sup>2</sup>Cardiology clinic, Clinical centre Niš, <sup>3</sup>Cardiology clinic, Clinical centre of Serbia; Medical faculty, University of Belgrade

## Abstract

COVID 19 infection in three phases: Phase I: Early infection, this phase is characterized with intrusion and direct invasion of COVID 19 into sensitive tissues. In this phase, virus is confronted only by the innate non-specific immunity. Symptoms are moderate in intensity. A more pronounced immune response is taking place, and in some cases a cessation of symptoms occurs. If the infection does not end here, a second phase develops. Phase II: pulmonary phase, pulmonary tissue invasion takes place and leads to direct tissue damage with added pulmonary vasodilation, enhanced endothelial permeability, leucocyte invasion as a cellular immune response to infection. This is clinically represented by further lung damage, and added burden on cardiovascular system. Phase III: Hyperinflammatory phase, this phase is presented as an escalation of immune response, which incorporates ARDS locally, acute myocardial damage, heart failure development, and systemic inflammatory response-multiorgan failure. This is complicated by secondary bacterial infection and enhanced intravascular coagulability. Arrhythmia is the most common, but also most benign cardiovascular complication in COVID 19 patients. Viral myocarditis, with heart failure elements, is a complication which has to be always thought of, especially in patients with unusually prolonged dyspnea. COVID 19 infection did not have a direct effect on coronary artery disease incidence, but on the other hand had a major effect on time to first contact of the patients with medical service and to the decision making in the treatment process.

**Key words** COVID-19, cardiovascular complications

## Introduction

Officially the first COVID 19 patient was registered in Serbia on March the 6<sup>th</sup> of 2020. The illness had a pandemic character with severe virulency but fortunately with fatality rate 2.2% of total number of cases<sup>1,2</sup>. COVID 19 got its name as an acronym from Corona Virus Disease detected in 2019. In this way a new breed of Corona virus was registered, out of already well-known family of Corona viruses which caused common cold syndrome. COVID 19 is characterized by high virulency, but 80% of patients have asymptomatic form or mild form of the disease<sup>1,2</sup>. The rest of them, 20%, require hospitalization<sup>1,2</sup>, and out of those most common presentation is of bilateral interstitial pneumonia, while 5-10% require some form of oxygen therapy and support. The data showed that patients with cardiovascular comorbidities had a greater chance of acquiring bilateral pneumonia, and on the other hand 25% of patients with pneumonia developed at least one cardiovascular complication. Out of those, some 26% were treated in intensive care unit<sup>3</sup>. Patients with preexisting cardiovascular comorbidities had a much worse prognosis in COVID 19 infection. The therapy used in COVID 19 patients is still very unspecific.

Unfortunately, there is no specific drug which is targeting the virus itself. Some antiviral drugs are used, like Aluvia (Kalitrea), well known anti-retroviral drug. Remdesivir is another drug that is utilizing viral RNK polymerase inhibition. It was developed as a treatment for Ebola infection, and showed somewhat more efficacy against COVID 19 than the other antiviral drugs. On the other hand, the latest WHO paper renounces the use of remdesivir as inefficient. Standard therapy of COVID 19 infection incorporates the use of antibiotics, but as treatment and/or prevention of bacterial superinfection.

## COVID-19 and cardiovascular complications

The main question is how this virus affects human body, and how we got from harmless virus, characterized by mild upper respiratory tract symptoms to this new form of Corona virus, which presents itself in some cases with severe bilateral interstitial pneumonia and sometimes very rapid development of ARDS with unpredictable outcome. Goha et al.<sup>5</sup>, divided COVID 19 infection in three phases:

Phase I: Early infection, this phase is characterized with intrusion and direct invasion of COVID 19 into sensitive

tissues. In this phase, virus is confronted only by the innate non-specific immunity. Symptoms are moderate in intensity. A more pronounced immune response is taking place, and in some cases a cessation of symptoms occurs. If the infection does not end here, a second phase develops.

Phase II: pulmonary phase, pulmonary tissue invasion takes place and leads to direct tissue damage with added pulmonary vasodilation, enhanced endothelial permeability, leucocyte invasion as a cellular immune response to infection. This is clinically represented by further lung damage, and added burden on cardiovascular system.

Phase III: Hyperinflammatory phase, this phase is presented as an escalation of immune response, which incorporates ARDS locally, acute myocardial damage, heart failure development, and systemic inflammatory response-multiorgan failure. This is complicated by secondary bacterial infection and enhanced intravascular coagulability.

Ma et al.<sup>6</sup>, describe the influence of COVID 19 infection on cardiovascular system as:

- Direct viral cell invasion
- Indirect damage-immune system mediated
- Large presence of proinflammatory cytokines
- Electrolyte and fluid retention
- Enhanced sympathetic activity
- Platelet activation and procoagulability
- Pneumonia-hypoxia

Data from Wuhan<sup>3</sup> showed that 16.7% of patients developed any form of arrhythmia, 7.2% acute coronary syndrome, and in some number of patients a Troponin increase was interpreted as a myocardial lesion due to myocarditis. Part of those patients developed heart failure symptoms.

Myocarditis represents virus invasion of cardiomyocytes with tissue destruction. The disease has its acute and chronic phase. The acute phase of myocarditis is consequence of direct cell invasion with virus particles which in turn leads to cardiomyocyte damage under the cytotoxic effects of the virus. On day 0. Of the infection, virus genome is being replicated inside the cardiomyocytes. This process is taking place during the first week, so on the 6<sup>th</sup> day it is in its peak. On the 10<sup>th</sup> day of the infection, replication ceases, as well as the direct cardiomyocyte damage caused by virus replication in it. In this phase, the clinical picture is oligosymptomatic. However, cardiomyocyte lesion is predisposing factor for starting humoral immune reaction to infection, and is practically followed by the chronic phase of myocarditis, characterized by autoimmune damage mediated by inflammatory cell invasion and autoantibody activation. An unspecific immune response, cellularly mediated is being activated, it incorporates activated leucocytes, lymphocytes (CD4, CD8), macrophages. These cells are directly damaging and destroying virus host cells, in this case cardiomyocytes, but also they are releasing a large quantity of inflammation factors and mediators, which in turn cause "Cytokine storm", on the other hand blamed to be the main mechanism of further destruction of the host cells after the virus itself. This phase can

last a variable amount of time, and is represented by the clinical presentation of myocarditis, but also sometimes with heart failure symptoms. This "Cytokine storm" is followed by the autoimmune response, mediated by the activation of the specific immune answer and the appearance of the antibodies to the virus particles, but also by the appearance of the cross reaction and development of the auto-antibodies to sarcolemma, myolemma, mitochondrial proteins, actin, myosin, collagen, and beta receptors. This mechanism leads to additional cardiomyocyte lesion, which can be clinically represented with mild, moderate or severe heart failure symptoms even weeks or month/s after the acute phase of the infection. A group of German authors followed 100 patients after resolved COVID 19 infection, out of which only 33% were hospitalized due to infection. All of those had a cardiac NMR done, after an average of 71 days after infection. 78% had pathological findings. This group of authors concluded that COVID 19 patients had to be monitored for their health condition for a long time after the infection resolves<sup>7</sup>. Other authors<sup>8</sup> have recorded that after discharge and successful COVID 19 treatment, often poor strain tolerance and chest oppression remain for a long time.

Heart failure was registered in 52% of the deceased and in 12% of discharged COVID 19 patients<sup>2,5</sup>. It is represented as an exacerbation of already existing heart failure, or like septic induced cardiomyopathy in myocarditis itself. In its most severe form, its presentation is a combination of septic and cardiogenic shock. The use of ACE inhibitors, or ARB blockers had its share of controversy tied to their influence to the infection and inflammation. Today's position on this subject is that the use of these medications is safe. The use of beta blockers in patients with pneumonia increased 30-day mortality and the need for mechanical ventilation.

Arrhythmias were the most common cardiovascular manifestations of COVID 19, and on the other hand most frequent of those is sinus tachycardia, symptomatic or asymptomatic. Arrhythmias "per se" are rare, mainly they were manifest in myocarditis, myocardial ischemia, hypoxia, shock, electrolyte disturbances or as a toxic reaction to the therapy (QT prolongation of the Chloroquine, or beta blocker use).

Coronary artery disease was a rare occurrence in COVID patients. However, in time of COVID pandemic, a change in therapeutic algorithms for STEMI patients took place, so that in USA, recommended mode of therapy for majority of the STEMI patients was pPCI, while fibrinolysis was still recommended as the first choice in uncomplicated inferior infarction without right ventricle affection<sup>9</sup>. In NSTEMI patients there were no changes in treatment protocols to that degree, so they were all medically (conservatively) treated. The patients with hemodynamic instability were treated with PCI. In turn, this strategy was more less the same before the COVID 19 pandemic. Out of pool of medications used in coronary artery disease treatment, statins stood out. The data showed that statins improve survival and also decrease systemic inflammation. The group of authors<sup>10</sup> showed that a combination of statins and ACEI improved

survival in COVID 19 patients and CAD. Almost all the authors and researchers concluded that the biggest issue in treating CAD patients during the pandemic was the delay from the symptom onset to the first medical contact<sup>11-12</sup>.

The therapy used in COVID 19 patients is still very un-specific. Unfortunately, there is no specific drug which is targeting the virus itself. Some antiviral drugs are used, like Aluvia (Kalitrea), well known anti-retroviral drug. Remdesivir is another drug that is utilizing viral RNK polymerase inhibition. It was developed as a treatment for Ebola infection, and showed somewhat more efficacy against COVID 19 than the other antiviral drugs. On the other hand, the latest WHO paper renounces the use of remdesivir as inefficient.

Standard therapy of COVID 19 infection incorporates the use of antibiotics, but as treatment and/or prevention of bacterial superinfection. However, high dosage antibiotics use is not without toxic effects. Macrolides can cause QT prolongation, hence having proarrhythmic effects and causing PVC's and tdp's. Vancomycin causes enhanced histamine liberation and thus hypotension. In the beginning all the treatment protocols incorporated Chloroquine as a standard non specific anti-inflammatory drug. However, its use in high doses caused cardiotoxicity with increased risk of heart failure and proarrhythmic effects. During the last months, corticosteroid use in high doses is more and more practiced, but based on experience with SARS, MERS, and influenza, there is no evidence for their beneficial effects<sup>13</sup>. The WHO position is that routine use of corticosteroids in COVID 19 patients is not recommended<sup>14</sup>.

## Conclusions

Arrhythmia is the most common, but also most benign cardiovascular complication in COVID 19 patients. Viral myocarditis, with heart failure elements, is a complication which has to be always thought of, especially in patients with unusually prolonged dyspnea. COVID 19 infection did not have a direct effect on coronary artery disease incidence, but on the other hand had a major effect on time to first contact of the patients with

medical service and to the decision making in the treatment process.

## References

1. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* 2020;34:1–7.
2. Long B, Brady WJ, Koyfman A, et al., Cardiovascular complications in COVID-19, *American Journal of Emergency Medicine*, <https://doi.org/10.1016/j.ajem.2020.04.048>
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus infected pneumonia in Wuhan. *JAMA* 2020.
4. Inciardi RM, Adamo M, Lupi L. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020;41:1821–9.
5. Goha A, Mezue K, Edwards P, et al. COVID 19 and the heart: An update for clinicians. *Clinical cardiology* Wiley. 2020. 1-7.
6. Ma L, Song K, Huang Y. COVID 19 and cardiovascular complications. *J Cardiothoracic Vasc Anesthesia* 2020.
7. Puntmann VO, Carerj L, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* doi:10.1001/jamacardio.2020.3557 Published online July 27, 2020.
8. Halpin SJ, Mclvor C, Whyatt G. Post discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2020;35:1–10.
9. Welt FGP, Shah PB, Aronow HD, et al. ACC, SCAI, Cath lab considerations during the COVID 19 pandemic. *J Am Coll Cardiol* 2020.
10. Mehra MR, Desai SS, Kuy DS. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med* 2020;382:e102. DOI: 10.1056/NEJMoa2007621.
11. Pessoa-Amorim G, Camm KF, Gajendragadkar P. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur Heart J* 2020. doi:10.1093/ehjqcco/qcaa046
12. Roffi M, Capodanno D, Windecker S, et al. Impact of the COVID-19 Pandemic on Interventional Cardiology Practice: Results of the EAPCI Survey. *EuroIntervention* 2020. doi: 10.4244/EIJ-D-20-00528.
13. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med.* 2006;3(9): e343.
14. World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Geneva: World Health Organization; 2020. [https://www.who.int/publicationsdetail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publicationsdetail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) (accessed March 30, 2020).

## Sažetak

### KARDIOVASKULARNE KOMPLIKACIJE KOD PACIJENATA SA COVID-19 INFEKCIJOM

Vladimir Mitov<sup>1</sup>, Aleksandar Jolić<sup>1</sup>, Dragana Adamović<sup>1</sup>, Milan Nikolić<sup>1</sup>, Marko Dimitrijević<sup>1</sup>, Tomislav Kostić<sup>2</sup>, Milan A. Nedeljković<sup>3</sup>

<sup>1</sup>Odeljenje Invazivne kardiologije, Medicinski centar Zaječar

<sup>2</sup>Klinika za Kardiologiju, Klinički centar Niš

<sup>3</sup>Klinika za Kardiologiju, Klinički centar Srbije; Medicinski fakultet, Univerzitet u Beogradu

COVID 19 infekciju su podelili u tri faze: **I FAZA-RANE INFEKCIJE**-Karakteriše se prodorom i direktnom invazijom tkiva COVID 19 virusom. U ovoj fazi virusu se telo odupire samo urođenim nespecifičnim imunitetom. Klinički se ispoljavaju simptomi koji su umerenog intenziteta. Dolazi do razvoja imunog odgovora zbog čega dolazi do opadanja broja virusa i u nekim slučajevima do prekida simptoma. U koliko se infekcija ne završi na ovom nivou razvija se druga faza: **II FAZA-PLUĆNA FAZA**-Invazija plućnog parenhima koja dovodi do direktnog oštećenja tkiva uz pridođatu plućnu vazodilataciju, povećane endotelne permeabilnosti i invazije leukocita kao odgovor celularnog imuniteta na infekciju. Klinički će se ispoljiti kao dalje oštećenje plućnog parenhima uz dodatno opterećenje kardiovaskularnog sistema. **III FAZA – HIPERINFLAMATORNA FAZA**-Eksacerbacija imunološkog odgovora što se klinički manifestuje, lokalno kao ARDS, akutno oštećenje miokarda, razvoja srčane slabosti i sistemskog odgovora u vidu multiorganske disfunkcije. Na ovo stanje se nadovezuje sekundarna bakterijska infekcija i pojačana intravaskularna koagulabilnost. **Terapija** COVID pacijenata je još uvek nespecifična. Ne postoji specifičan lek koji etiološki deluje na ovaj virus. Koriste se antivrotici Aluvia (Kalitrea), od ranije poznat lek za RNK viruse. Remdesivir je drugi antivrotik koji kao prolek inhibira virusnu RNK polimerazu. Razvijen je kao lek za ebolu a pokazao se efikasniji od ostalih antivrotika. Najbliža specifičnoj terapiji je upotreba gotovih antitela iz plazme pacijenata koji su preboleli COVID infekciju. U standardnoj terapiji COVID pacijenata je upotreba i antibiotika, pre svega kao terapija bakterijske superinfekcije. Aritmije su najčešća ali i najbezopasnija kardiovaskularna stanja u COVID 19 pacijenata. Virusni miokarditis sa elementima srčane slabosti je kardiovaskularna komplikacija o kojoj treba misliti posebno kod pacijenata sa dispneom koja neuobičajeno dugo traje. COVID 19 infekcija nije direktno uticala na incidencu koronarne bolesti, međutim značajno je uticala na vreme prijema pacijenata i odluku o načinima lečenja.

**Ključne reči:** COVID-19, kardiovaskularne komplikacije