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COMPREHENSIVE VIEW OF CARDIOVASCULAR COMPLICATIONS IN SARS-COV-2 INFECTION

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Abstract: The disease caused by the new coronavirus has established itself as an important global pandemic, as it spread across world borders and, with that, quickly became the greatest medical challenge of the last century. SARS-Cov-2 invades cells through the angiotensin-converting enzyme 2 (ACE2) receptor, causing significant cardiopulmonary impairment. Thus, acute myocardial injury, myocarditis, arrhythmias, thromboembolic events, ACS, endothelial dysfunction, heart failure, and even sudden cardiac death, are events that can occur secondary to an infection by the Covid-19 virus and cause significant impacts on the prognosis. of our patients. This review seeks to elucidate the mechanisms of cardiac injury, in the face of infection with the new coronavirus, to analyze the most frequent cardiovascular complications, as well as their stratification, their respective management, and also to highlight the importance of an integral and individualized approach, through the adoption of the cardiovigilance of patients, from diagnosis to complete recovery.
Keywords: Complications, mechanisms, injury, cardiovascular, Covid-19 and SARS-Cov-2.

INTRODUCTION

The pandemic associated with SARS-CoV-2 infection has established itself as an unprecedented challenge in the history of modern health, causing a palpable health collapse in many countries. The first confirmed and documented case of the disease occurred in Hubei province in China in December 2019, today (July 15, 2022), the disease has already been confirmed and documented more than 562 million times. Like other coronaviruses, this disease has frequent symptoms: fever, cough, dyspnea, lower tolerance to exertion, headache, fatigue, asthenia, diarrhea, nausea and vomiting. However, the cardiovascular complications caused by this disease are also the target of great emphasis, since in addition to having a high prevalence, they are also related to a worse prognosis.

SARS-CoV-2 has a much higher transmissibility than other coronaviruses, which contributed to the spread of the infection up to ten times faster. SARS-CoV-2 infection is marked by the development of numerous injury mechanisms, such as direct injuries, systemic inflammation, cytokine storm, endothelial dysfunction, hypoxemia, oxidative stress, increased thromboembolic potential, among others. These mechanisms act synergistically, causing significant damage to cardiomyocytes. Therefore, the deleterious effects caused by SARS-CoV-2 are not limited to the pulmonary scope, being capable of generating complications such as: myocardial injury, myocarditis, arrhythmias, thromboembolic events, ACS, microvascular diseases, HF, cardiogenic shock, failure of multiple organs and MSC. Such a scenario makes the rapid diagnosis and rapid stratification of these cardiovascular complications essential.

INFECTION MECHANISM

SARS-Cov-2 is a single-stranded RNA-virus enveloped with the Spike protein, which has the greatest emphasis on the infectious process. In this process, the Spike protein is activated by its cleavage, provided by the transmembrane serine protease 2 (TMPRSS2), which is widely distributed in our cells.

Subsequent to this activation, the binding of the Spike protein to the ACE2 receptor occurs, enabling the internalization of this virus. It is not uncommon for cell groups marked by the co-expression of TMPRSS2 and ACE2 to be the main targets of SARS-Cov-2, largely affecting type II pneumocytes, alveolar macrophages, cardiomyocytes, vascular endothelium, glomerular cells, among others, which exposes patients to a multisystemic

disease and even to the risk of multiple organ failure in the most severe cases.

Subsequently, it must be noted that ACE2 is responsible for converting angiotensin II into peptides with less activity, to prevent excessive and harmful stimulation of the CV system. This scenario makes it clear that the association of the viral SPIKE protein with ACE II is extremely harmful, since in addition to allowing viral internalization, it also causes a downregulation of ACE2, which culminates in great fragility of the mechanisms of suppression of the renin- angiotensin-aldosterone (RAAS).

RISK FACTORS ASSOCIATED WITH THE PATHOGENESIS OF COVID-19

It was consolidated as irrefutable the fact that patients with CVD prior to infection have a higher risk of being more vulnerable to contamination by SARS-Cov-2 and developing a more severe disease. This scenario occurs because in states with excessive RAAS activation, such as SAH, HF and atherosclerosis, there is a significant increase in ACE2 expression in cardiomyocytes and endothelial cells, in order to intensify its protective effect on the cardiovascular system, increasing the rate of infection by the SARS-CoV-2 and enhancing the development of injury mechanisms associated with cardiovascular complications. Not infrequently, patients with SAH, DM, obesity, other CVDs, dyslipidemia and atherosclerosis (20%) were the target of a greater development of serious diseases and mortality.

Furthermore, it must be noted that older age (over 60 years) and neoplasms are also risk predictors for the development of CV complications.

MECHANISMS OF MYOCARDIAL INJURY

The cardiovascular system can be severely affected by different injury mechanisms that can be established with the progression of this disease. Such mechanisms develop as SARS-Cov-2 expresses its high harmful potential, compromising the respiratory tract and generating an exacerbated local and systemic inflammatory response, vascular inflammation, an important state of hypercoagulability and weakening of the cardiopulmonary protective effect exerted by ACE2.

This scenario, in turn, consolidates with greater impact and intensity in those patients who present the risk factors presented, making them susceptible to the development of more severe conditions and thus justifying the exposure of such patients to the greater elevation of the cardiac (such as Tn and NT-proBNP/BNP) and inflammatory biomarkers (such as D-Dimer, C-Reactive Protein, procalcitonin, LDH, IL-6, ferritin) and greater functional and structural impairment evidenced on the Echocardiogram, through the decrease in LVEF and cardiac chamber dilation, especially in patients admitted to the ICU or who died.

In a meta-analysis of four studies including a total of 341 patients, troponin I levels were significantly higher in those with the severe form of COVID-19 compared to those with the non-severe form. Furthermore, patients with myocardial injury were hospitalized more in the intensive care unit (ICU) (22.2% vs. 2.0%), had a higher incidence of HF (52% vs. 12%) and a higher death rate (59% vs. 1%).

Therefore, it is extremely important to understand what are the main mechanisms of myocardial injury, capable of generating these precarious prognoses:

1) Direct myocardial injury: As previously mentioned, the high expression of TMPRSS2

and ACE2 enzymes in cardiomyocytes and lung cells make these the main sites of infection by SARS-Cov-2. Furthermore, the binding that occurs between ACE2 and the viral Spike protein causes a major alteration in the neurohumoral regulation carried out by this enzyme, generating important acute myocardial injuries and lung damage (generally concomitant). A great example of this type of injury is present in the fact that the binding that occurs between such proteins is closely related to the Down-Regulation of the ACE 2 enzymes, making it unable to act in the conversion of angiotensin II into other peptides of lesser activity, there is soon an extreme potentiation of the effects associated with the RAAS, which exposes patients with Covid-19 to deleterious effects on the cardiovascular (CV) system, such as: excessive vasoconstriction, increased sympathetic tonus, hypervolemia, hypokalemia, among others.

2) Systemic inflammation associated with cytokine storm: In synergy with the mechanism of direct injury, the hyper-inflammatory state and cytokine storm are the main mechanisms of myocardial injury and have an important relationship with worse prognosis. SARS-CoV-2, after binding to ACE2 and other membrane receptors, promotes rapid activation of Th1 cells and thereby stimulates large production of cytokines such as GM-CSF and IL-6. The former starts to stimulate inflammatory monocytes that increase the synthesis of IL-6, TNF-α and several other cytokines. This entire inflammatory state and hypercytokinemia results in the formation of an extensive inflammatory infiltrate in the lung tissue, endothelial damage, myocardial aggression and even multiple organ damage. It is not uncommon for patients with systemic inflammation associated with cytokine storms to be exposed to higher rates of severe illness with ICU admission, HF, arrhythmias, MV (mechanical ventilation), multiple organ failure and death.

3) Acute respiratory failure associated with an imbalance between oxygen supply and demand, hypoxemia and increased oxidative stress: Parallel to the development of such a systemic inflammatory state with great hypercoagulability, we observe a large increase in cardiometabolic demand, which is inefficiently compensated due to concomitant pulmonary impairment. Thus, an important hypoxemic state and greater oxidative stress are installed, which culminate in the intensification of the injury and myocardial damage.

4) Endothelial damage and increased atherothrombogenic potential: A healthy endothelium is closely linked to the maintenance of cardiovascular homeostasis, as it prevents the adhesion and aggregation of blood cells, inhibits pathological intimal medium hyperplasia, regulates blood supply to each tissue, maintains relaxation of the smooth muscles of blood vessels by producing of vasodilating substances such as nitric oxide and prostacyclin, and still allows high efficiency in the exchange of substances between blood and tissues. Often, it is critical in maintaining the structure and function of the cardiovascular system.

- In Covid-19, direct injury and the cytokine storm damage the endothelium. This scenario causes several changes in endothelial function, since it compromises the control of vasodilation, reducing the synthesis and secretion of nitric oxide (NO) and prostacyclin (PGI2), causes dysfunction of the glycocalyx present in endothelial cells - which would be responsible for create a barrier against the aggregation of platelets and blood cells - and even increases the expression of endothelial adhesion molecules and

inflammatory cytokines, factors that culminate in a great increase in damage and local inflammation.

- Furthermore, it must also be noted that in Covid-19, this whole scenario marked by endothelial damage, the cytokine storm and the imbalance between vasoconstrictors and vasodilators, is still added to the effects of sepsis, acute respiratory distress syndrome and the extensive consumption of coagulation systems, causing patients to be exposed to a high state of hypercoagulability and even disseminated intravascular coagulation (DIC). Not infrequently, patients infected with SARS-CoV-2 can develop significant vascular complications, which in turn can suddenly affect different vascular beds, which can promote pulmonary inflammation and edema, microvascular inflammation and myocarditis, coronary thrombosis, AMI, carotid thrombosis, cerebrovascular diseases, local ischemia, DVT, PTE and other manifestations and sequelae related to this large increase in atherothrombogenic potential.

5) Hydroelectrolytic imbalance: They have an intrinsic relationship with numerous systemic diseases and can precipitate important arrhythmias, especially in patients already exposed to myocardial disorders caused by SARS-Cov-2 itself or by the risk factors, previously presented. In Covid-19, hypokalemia must be emphasized, which occurs secondary to the changes caused in the RAAS and significantly increases the risk of tachyarrhythmias.

6) Adverse effects associated with different therapies: *Several antiviral drugs, corticosteroids and other therapies used in the treatment of Covid-19 can contribute to deleterious effects on the cardiovascular system.*

THE USE OF BIOMARKERS IN COVID-19 INFECTION

In convergence with the consolidation of these numerous injury mechanisms, myocardial injury biomarkers (TnT, NT-Pro-BNP/BNP) and inflammatory biomarkers (CRP, D-dimer, ESR, IL-6, Ferritin) gain great prominence in the assessment of patients with Covid-19,. Thus, it must be noted that there were numerous studies, which made it clear that these markers are often higher in patients with the risk factors mentioned above, which directly corroborates the fact that these patients are more frequently exposed to the development of severe disease with cardiovascular complications. Furthermore, these studies also highlighted that only TnT and CRP were confirmed as independent risk predictors for contracting a disease susceptible to worse outcomes, such as: the development of malignant arrhythmias (ventricular tachycardia with degeneration to ventricular fibrillation or hemodynamic instability), the need for ICU admission and MV, the development or exacerbation of HF and death. However, the other markers can also offer us valuable information regarding the clinical scenario involving our patient, since, together with TnT and CRP, they help us to stratify and understand the degree of systemic involvement and the prognostic evolution of each individual.

The fact that a patient has an increase in NT-Pro-BNP/BNP, especially if he has risk factors, makes a thorough assessment of cardiac function necessary, since it can be an important predictor of severe myocardial injury, secondary to the effects of different injury mechanisms. Those patients with increased CRP and D-Dimer, however, need careful stratification of their risk of developing thromboembolic events, since in any type of

risk, they will become important candidates for therapies with anticoagulants.

These situations are built as some examples that share the proposal that, if compatible with the service in which the patient is inserted, it is extremely important to carry out a comprehensive assessment of biomarkers, even if only TnT and CRP are predictors independent for the risk of poor outcomes. This occurs because this type of evaluation can help us to identify patients susceptible to an unfavorable clinical evolution and, therefore, to implement more effective individualized conducts with an early approach to possible complications.

THE ROLE OF ECG AND ECHO

Furthermore, in addition to biomarkers, other evaluation methods are also essential so that we can carry out a comprehensive and early study of cardiovascular complications that may be based on the different injury mechanisms present in the disease in question.

Initially, it is essential that, together with the biomarkers, an extensive electrocardiographic evaluation be carried out, since this resource is also an important predictor of cardiovascular injury. Not infrequently, the most prevalent cardiovascular complication (acute myocardial injury) can be determined either by the elevation of troponins above p99, or by the presence of acute changes in the ECG, being a tool of great help in identifying patients at high cardiovascular risk and contributing to the decision of hospitalization and management of the case.

In addition, the use of ECG in the periodic evaluation of patients with moderate or severe diseases can also identify, early on, important malignant arrhythmias (which have a high potential to progress with severe hemodynamic instability), and ischemia (associated with thromboembolic events, myocarditis, systemic inflammation, and greatly increased metabolic demand).

As for the transthoracic ECHO, it must be noted that its use is reserved for those patients who, in general, will be candidates for hospitalization, such as patients with more severe symptoms or the presence of symptomatic conditions in patients subject to risk factors for the development of complications cardiovascular. This exam demonstrates the systolic and/or diastolic compromise of the ventricles, provides hemodynamic information that helps in the management of patients and even indicates the presence of pericardial alterations.

Furthermore, in addition to basing ourselves on the severity of the disease, on previous risk factors and on laboratory tests, in order to indicate the performance of the transthoracic ECHO, we must also request it in case the patients present clinical signs of certain pathologies that can cause rapid deterioration of the prognosis, such as: heart failure, acute coronary syndrome, hemodynamic instability, myocarditis, pulmonary embolism, clinically relevant arrhythmias, pericardial effusion, endocarditis, syncope and cardioembolic source of stroke.

Therefore, the correct indication of this exam is essential so that we can offer a comprehensive evaluation of the disease of our patients. This occurs because the echocardiographic findings must be considered before adopting each approach, since episodes marked by RV dilation and hypokinesia, hemodynamic compromise, biventricular dysfunction or LV systolic dysfunction are important predictors of these patients' exposure to valve lesions., renal impairment, pulmonary thromboembolism, MV and death. Often, like the other tests mentioned above, the transthoracic ECHO is also very important in the disease stratification process of our patients, and allows us to offer intensive care and treatment to these

patients, who are potential targets for rapid decompensation. cardiopulmonary.

CARDIOVASCULAR COMPLICATIONS

The various systemic complications that go hand in hand with the worsening of the disease are direct consequences of the progression of the numerous injury mechanisms associated with this disease, affecting mostly patients with the risk factors presented. In particular, CV complications gain great emphasis in this disease, due to their significant prevalence and their negative impact on patient morbidity and mortality.

1) Myocarditis: Myocarditis is the most prevalent complication, affecting approximately 8% to 12% of positive cases. It presents with clinical pictures that can be widely heterogeneous, since they can manifest with chest pain, dyspnea, arrhythmias, fever and some degree of ventricular dysfunction.

In general, it is defined by the elevation of ultrasensitive troponin, above p99, but it must also be considered in the presence of electrocardiographic alterations. The presence of such an acute injury, in turn, is closely related to increased rates of ICU admission, MV, HF, arrhythmias, cerebrovascular diseases and death. Thus, the measurement of biomarkers and electrocardiographic monitoring in patients who already have risk factors or moderate disease is essential, so that we can adopt an early and effective approach.

Furthermore, it must be noted that the development of myocarditis occurs from the consolidation of important harmful mechanisms, such as direct injury by SARS-CoV-2, systemic inflammation associated with the cytokine storm and the imbalance between supply and demand of oxygen with hypoxemia and increased oxidative stress.

Therefore, this complication, in addition to being highly prevalent and deleterious, also leads to the development of other more serious complications such as AMI. This, in turn, marks a greater presence as its type II, which does not present rupture of the atheromatous plaque and is a direct consequence of the imbalance between oxygen supply and demand (MINOCA).

1.1) Microvascular injury: Another probable mechanism of myocardial injury stems from the formation of microthrombi in the myocardial vasculature, due to exposure to hypercoagulability and disseminated intravascular coagulation (DIC), intensified by the state of systemic inflammation and the cytokine storm.

Therefore, alterations in the coagulation and fibrinolytic systems are significantly present in patients with COVID-19, determining a broad homeostatic imbalance, which makes these individuals highly vulnerable to microvasculature impairment, which can cause significant and even irreversible damage. heart muscle and other body tissues.

Therefore, the early detection of these disorders and, mainly, the introduction of prophylaxis measures for patients with more important clinical conditions or with risk factors, it is essential to guarantee a better prognosis for our patients.

1.2) Stress Cardiomyopathy (Takotsubo Syndrome): DuringtheSARS-CoV-2pandemic, there was an approximately five-fold increase in the incidence of Takotsubo syndrome. The pathophysiological mechanisms associated with this increase may be a direct result of the virus, causing a myocarditis that mimics Takotsubo (Takotsubo –like cardiomyopathy) or, more likely, the effect of the psychological stress imposed by the quarantine and the risk of the pandemic, the loss of interaction caused by distancing rules or the socioeconomic consequences of the pandemic, especially when associated with the contraction of the disease, being still exposed to microvascular

dysfunction, cytokine storm, impaired ability to meet cardiometabolic demand and increased sympathetic tone.

2) Arrhythmias: Throughout the Covid-19 pandemic, several cases of changes in heart rhythm were recorded, with a clear predominance of tachyarrhythmias. Not infrequently, complaints of palpitations and chest pain were very frequent in the consultations.

In patients infected with SARS-CoV-2, several arrhythmogenic predisposing factors were present, as well as hydroelectrolytic disorders (especially hypokalemia), hypoxemia, shock, myocarditis, myocardial injuries and ischemic components, and even side effects associated with pharmacological therapies.

In general, arrhythmias affected approximately 8% of positive cases, but with a large increase in this incidence, when considering patients admitted to the ICU, reaching approximately 40% of cases.

The most commonly observed rhythms were sinus tachycardias, supraventricular arrhythmias, atrial fibrillation, atrial flutter and even malignant arrhythmias (ventricular tachycardias and ventricular fibrillation), which occur in about 10% of hospitalized patients. Therefore, it is mandatory to perform an ECG in patients who are hospitalized due to Covid-19, and in cases of confirmed arrhythmia, the evaluation of ventricular function is also indicated by means of a transthoracic echocardiogram and the elaboration of a plan of individualized action, aiming at an early treatment and maintenance of hemodynamic stability.

3) Thromboembolic events: The extensive endothelial damage linked to systemic inflammation, the cytokine storm and, therefore, to DIC and thrombotic microangiopathy, meant that patients affected by more significant and prolonged conditions of Covid-19 were affected by an important coagulopathy which affects both venous and arterial circulation. Thus, there were numerous manifestations of these events, including PTE, DVT, stroke and even cases of peripheral arterial occlusive disease.

Furthermore, it must be noted that the pathophysiology of systemic inflammation, cytokine storm and endothelial damage is constantly exposed to prolonged rest, commonly indicated for patients with COVID. Such a scenario meant that the vast majority of patients were completely affected by Virchow's Triad (Hypercoagulability, stasis and endothelial dysfunction).

Thus, the position of thromboembolic events as important cardiovascular complications of SARS-CoV-2 and as great predictors of higher mortality is undoubted, requiring early and effective prevention, diagnosis and treatment, so that, in this way, we can avoid its sequelae and reduce its fatality rate.

***4) Heart failure*:** HF can represent both a risk factor for a worse infectious evolution and a serious cardiovascular complication caused by the SARS-CoV-2 virus, however, regardless of this, the simple presence of HF in the context of COVID-19 identifies a subgroup with complex management and higher morbidity and mortality. Often, HF affects about 50% of deaths, while it is present in only 10% to 15% of survivors, data that directly corroborate the fact that patients who have high levels of cardiac biomarkers (NT -Pro-BNP and TnT) are more susceptible to unfavorable outcomes.

In this context, the predisposition to the emergence of a new acute or chronic acute HF is a consequence of the consolidation of a synergistic action between injury mechanisms, such as direct injury to cardiomyocytes, hyperactivation of the inflammatory cascade, hyperstimulation of the neurohumoral

system, cytokine storm, endothelial damage, ischemic events and limited ability to meet the increased cardiometabolic demand.

Finally, for patients with previous HF and suspected SARS-CoV-2 infection, we must carry out the investigation of these diseases as soon as possible, so that, in case of confirmation, immediate hospitalization is carried out in order to quickly adopt a treatment regimen. laboratory, echocardiographic and radiological monitoring, along with optimized treatment, acting with the same agility for patients who begin to indicate changes suggestive of a new acute HF in laboratory tests.

GENERAL MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS

From the consolidation of this scenario, it becomes evident that cardiovascular complications have a significant impact on patients infected with SARS-CoV-2. Thus, it is imperative that the team of cardiologists be part of the critical patient care team, thereby ensuring greater effectiveness in the treatment of these complications.

In addition to these patients with severe conditions, cardiovascular assessment must also be applied to a) patients who have preexisting CVD or cardiovascular risk factors; b) patients who present cardiovascular signs and symptoms (dyspnea, shock, precordial pain, electrocardiographic alteration or increase in cardiac area); and c) presence of changes in biomarkers such as TnT, PCR, NT-proBNP, D-dimer, ferritin and IL-6.

This assessment is initially carried out with a detailed anamnesis and physical examination of all patients with suspected or confirmed disease, always placing great emphasis on investigating the symptomatology, the presence of cardiovascular symptoms and the main risk factors that may cooperate with the development of cardiovascular complications, such as: SAH, HF, atherosclerosis, Diabetes Mellitus, cardiomyopathies, metabolic syndrome, obesity, smoking, alcoholism, sedentary lifestyle, chronic kidney disease, Chagas disease, advanced age, and cancer.

After this general evaluation, we will continue with the evaluation of these patients, based on the frequent use of complementary exams, which must be selected based on the data acquired in the anamnesis and in the physical examination performed.

In a first moment, we must evaluate the blood count, biomarkers (TnT, CRP and, if possible, NT-Pro-BNP, D-Dimer, Ferritin and IL-6), liver and kidney function, electrolytes, creatine phosphokinase, coagulogram, ECG and chest X-ray.

If this initial assessment shows alterations that may indicate cardiovascular and/or pulmonary impairment, we must proceed with an immediate request for an echocardiogram and/or chest CT, as they allow us to infer with greater sensitivity the extent of the structural and functional impairment of these systems.

Furthermore, it is still necessary to consider the request for cardiac magnetic resonance imaging (CMR), which can be a very important instrument in determining the diagnosis of the etiology of ventricular dysfunction, managing to provide us with detailed data on myocarditis or on induced systolic dysfunction by stress and ischemia.

From this initial approach, we can correctly stratify our patients and thus offer individualized treatment to each one of them. Thus, initially we must divide the patients into two larger groups, which will subsequently be fragmented into more specific groups. However, prior to adopting any approach, it is important to bear in mind that Covid-19 presents a broad clinical picture marked by significant variability. Therefore, even those patients with mild constitutional symptoms (such as fever, cough, fatigue, asthenia) must

be submitted to the initial approach mentioned above, with a detailed anamnesis and physical examination, and we must always give great emphasis to the investigation of the factors of risk and the early identification of signs of hemodynamic instability, since these must be immediately corrected with early measures of: invasive or non-invasive oxygen therapy, maintenance of blood volume (with careful monitoring, to avoid excessive administration of fluids, since they can cause congestion important), ECMO, heart rhythm control, among others.

1) Patients without risk factors

1.1) With mild symptoms

After the complete initial assessment with detailed anamnesis and physical examination, we will be able to discharge these individuals, with symptomatic treatment and guidance on social isolation, both for the patient and the contacts, and also provide guidance on relative rest, taking into account the patient's exposure on Virchow's triad. Therefore, for a better care of these patients, we must give detailed instructions about the signs and symptoms of thromboembolic events and hemodynamic instabilities, so that they return early, in case of deterioration of their clinical status.

1.2) With moderate or severe symptoms

The fact that these patients present important clinical conditions, already at an early stage, makes them the target of worse prognoses, even without presenting risk factors. Therefore, we must proceed with the hospitalization and request the entire routine of complementary tests mentioned above (hemogram, ECG, chest X-ray, TnT, CRP and, if possible, ESR, NT-Pro-BNP, D-Dimer, Ferritin and IL-6), liver and kidney function, electrolytes, creatine kinase, coagulogram.)

1.2.1) If the exams do not show alterations, we must only adopt the usual care, with treatment of constitutional symptoms and keeping this patient in isolation, with monitoring in a hospital bed, to follow its evolution and be able to act, early, in case of worsening important part of the clinical condition or discharge if the condition improves.

1.2.2) If the ECG and biomarkers show alterations, we must keep this patient in isolation in the ICU, under intensive care, with constant monitoring, periodic cardiac evaluation and request the ECO. In addition, we must still consider the use of MV for those patients who persist with significant hypoxemia (Sat O2<92%) despite the supply of oxygen and also adopt hemodynamic monitoring in patients with signs of shock or ventricular dysfunction, since this This evaluation may indicate an early initiation of Norepinephrine, associated or not with vasopressin, and, therefore, reduce the clinical deterioration of this patient.

2) Patients with risk factors

2.1) With mild symptoms

The fact that these patients are exposed to a greater chance of progressing with a rapid impairment of their clinical status, makes it necessary to associate their initial assessment with the request for the entire routine of complementary tests mentioned above.

2.1.1) If ECG and biomarkers do not show changes, we must consider hospital discharge. If it is safe to discharge the patient, we must proceed with the treatment of symptoms, guidance on social isolation for the patient and those in contact, advise on relative rest (taking into account the patient's exposure to Virchow's triad) and advise on the importance of outpatient reassessment or seeking emergency assistance in any changes or intensification of his clinical condition, since he has risk factors that can cause the disease to deteriorate quickly.

2.1.2) If the ECG and biomarkers show alterations, we must keep this patient in isolation in the ICU, under intensive care,

with constant monitoring, periodic cardiac evaluation and perform the ECHO request, even if the patients present clinical stability, as the fact that they have risk factors already exposes them to a greater chance of developing functional impairments of the heart and, therefore, a rapid deterioration of their prognosis. In addition, we must still consider the use of MV for those patients who persist with significant hypoxemia (Sat O2<92%) despite the supply of oxygen and also adopt hemodynamic monitoring in patients with signs of shock or ventricular dysfunction, since this This evaluation may indicate an early initiation of Norepinephrine, associated or not with vasopressin, and, therefore, reduce the clinical deterioration of this patient.

2.2) With moderate or severe symptoms

The fact that these individuals have risk factors that share the development and progression of cardiovascular complications and still develop a significant and early clinical course makes them patients subject to a delicate prognosis and very susceptible to poor clinical evolution. Often, in addition to the initial assessment and the usual request for laboratory tests, ECG and chest X-ray, we must request an ECHO, as it can provide us with important information about the cardiovascular impairment and guide a better approach.

2.2.1) If the requested exams do not show changes, we must hospitalize the patient, to monitor the patient's evolution and maintain periodic cardiac evaluation, and in the case of any changes in the clinical picture, it becomes important to carry out new tests exams and consider admitting a patient to the ICU.

2.2.2) If the exams present alterations, we must keep this patient in isolation in the ICU, under intensive care, with constant monitoring, periodic cardiac evaluation and daily echocardiograms. In addition, we must still consider the use of MV for those patients who persist with significant hypoxemia (Sat O2<92%) despite the supply of oxygen, and also adopt hemodynamic monitoring in patients with signs of shock or ventricular dysfunction, since this evaluation may indicate an early initiation of Norepinephrine, associated or not with vasopressin, and, therefore, reduce the clinical deterioration of this patient.

SPECIFIC APPROACH TO CV COMPLICATIONS

1) Endothelial dysfunction: Although this phenomenon is closely correlated with numerous of the topics that will be addressed here, it deserves special attention, since it corroborates with the development and evolution of various events and complications associated with the coronavirus. Consolidation of endotheliopathy is closely linked to the evolution of the hyper-inflammatory response, the cytokine storm and the hypercoagulable state, making it an important risk factor for increased metabolic demand and blood pressure, intensification of atherosclerosis, fibrogenesis and vascular and valve calcinogenesis, development of thromboembolic events and even increased tissue injury, secondary to acute inflammation. Often, control of endothelial dysfunction is essential. Thus, for patients with a more important clinical condition and with the aforementioned risk factors, we must seek strict control of the state of hyperinflammation and the cytokine storm, in addition to considering the adoption of drugs aimed at controlling the endotheliopathy, such as: ACE inhibitors/ ARBs, statins and even vasodilators.

2) Myocarditis, systemic inflammation and the cytokine storm: In order to be able to address acute myocardial injuries in a comprehensive way, it is necessary to reinforce that Covid-19 is an essentially systemic pathology, therefore it is of the

utmost importance that we maintain the monitoring of patients, addressing, early any signs of instability. Subsequently, it must be noted that both myocarditis and other diffuse tissue lesions that may occur in this pathology are severely aggravated by the hyper-inflammatory state and by the cytokine storm. Not infrequently, patients with more critical clinical conditions and with indicators of myocarditis and/or systemic inflammation with significant elevation of serum cytokines may benefit from starting therapy with glucocorticoids (prednisolone and methylprednisolone pulses), IL- 6 (tocilizumab) and even intravenous immunoglobulins, and these classes can still be associated in highly severe cases, such as extensive pulmonary fibrosis or fulminant myocarditis.

3) Thromboembolic events: The fact that patients infected with SARS-CoV-2 are the target of the cytokine storm, the hyper-inflammatory state and endothelial damage has made thromboembolic events the target of great medical attention, since they are related with poor outcomes and significant sequelae. Therefore, all hospitalized patients must receive therapy with unfractionated heparin or low molecular weight heparin as a way to prevent these events. As for patients with mild conditions and without risk factors, since they are not the target of biomarkers investigation, they must be instructed about general symptoms of thromboembolic events, since they can occur even in asymptomatic patients.

Furthermore, in addition to this general management, we must also emphasize that there may be multiple complications and sequelae secondary to thromboembolic events. Not infrequently, clinical investigation with anamnesis and physical examination of patients with Covid-19 must be thorough, in order to detect early signs and symptoms related to the consequences of endothelial damage.

4) Acute myocardial infarction: Although AMI has a great relationship with thromboembolic events, we must analyze it even more broadly and thoroughly in COVID-19. Often, investigation and definition of the etiology of AMI in Covid-19 is very important, since the increase in cardiometabolic demand - which is inefficiently compensated due to concomitant cardiopulmonary impairment - has caused the number of type II AMIs, after the onset of this pandemic, grew significantly. Such patients, in turn, may be submitted to more conservative approaches, when compared to the procedures we take in the case of the diagnosis of a type I AMI. Therefore, we must seek this stratification, in order to offer individualized treatments with greater efficacy and safety for each case, since we are dealing with critically ill patients who are more susceptible to the complications that can occur in some more invasive measures.

5) Arrhythmias: As for the management of arrhythmias, it must be noted that it must be based on current guidelines. However, it is important for us to be aware that the presence of this pathology is closely associated with thromboembolic events and worse outcomes. Therefore, the best conduct regarding arrhythmias is the search for their early diagnosis, through the early performance of the ECG, a cheap, fast and highly sensitive test.

6) Heart failure: As demonstrated in the previous topics, this pathology is intrinsically associated with a greater susceptibility to the development of adverse events. Thus, the best management route that we can adopt is with an early hospitalization of this patient, with optimization of the HF treatment and consolidation of a detailed cardiovascular evaluation routine, being essential the

periodic request of the following exams: NT-ProBNP/BNP, Troponins, CRP, D-Dimer, VHS, Ferritin, IL-6, Complete blood count, Creatinine and Urea to assess renal function, ECG, chest X-ray, transthoracic ECHO and even more specialized exams for individualized situations, such as chest CT in cases of pulmonary congestion and CMR in case of clinical deterioration or hemodynamic instability. Since it is extremely important that we are aware of the actual stratification of the HF stage of this patient, so that we can act, early, in case of exacerbation or clinical deterioration.

7) Cardiopulmonary arrest (CPR): In situations where patients with Covid-19 evolve with CRA, it is of paramount importance that any health professionals who will work in cardiopulmonary resuscitation (CPR) have adhered, in detail, to the protective measures individual, since CPR has a high potential for contamination, exposing the medical team to great risk. It is also up to these professionals to avoid maneuvers such as the use of bag-mask ventilation or endotracheal bag-tube, since they can be easily replaced by other effective conducts with less risk of contamination.

Therefore, the adoption of these measures is essential, as in addition to offering greater protection to our professionals, it also allows us to act early in these episodes, offering the best care for each patient.

CONCLUSION

Many of the intrinsic characteristics of SARS-CoV-2 have enabled this virus to rapidly spread across world borders, causing extensive cardiopulmonary involvement in many individuals. The development of cardiovascular complications in cases of coronavirus infection is directly related to a worse prognosis, causing these patients to be exposed to a higher risk of ICU admissions, MV, HF, arrhythmias, cerebrovascular sequelae and SCD. Thus, it is imperative that every health professional is fully aware of the possible consequences of this disease, knowing how to identify and address them early and effectively.

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