Wien Klin Wochenschr (2021) 133:1289–1297
https://doi.org/10.1007/s00508-021-01956-2

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Direct cardiovascular complications and indirect collateral damage during the COVID-19 pandemic

A review

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Received: 9 June 2021 / Accepted: 18 September 2021 / Published online: 20 October 2021

Summary The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), puts a heavy strain on healthcare systems around the globe with high numbers of infected patients. Pre-existing cardiovascular disease is a major risk factor for a severe clinical course of COVID-19 and is associated with adverse outcome. COVID-19 may directly exacerbate underlying heart disease and is frequently aggravated by cardiovascular complications, including arterial and venous thromboembolic events, malignant arrhythmia and myocardial injury. In addition to these direct cardiac manifestations of COVID-19, patients with cardiovascular disease face further indirect consequences of the pandemic, as the respective resources in the healthcare systems need to be redirected to cope with the high numbers of infected patients. Consecutively, a substantial decrease in cardiac procedures was reported during the pandemic with lower numbers of coronary angiographies and device implantations worldwide. As a consequence an increased number of out-of-hospital cardiac arrests, late-comers with subacute myocardial infarction and of patients presenting in cardiogenic shock or preshock were observed. Maintenance of high-quality cardiac care by avoiding a reduction of cardiac services is of utmost importance, especially in times of a pandemic.

Keywords Venous thromboembolism · Myocarditis · Arrhythmia · Interventional procedure · Acute coronary syndrome

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Introduction

The coronavirus disease 2019 (COVID-19) caused a global pandemic with more than 140 million patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in more than 200 countries worldwide [1]. Patients with a history of cardiovascular disease represent a particularly vulnerable group with a high risk of a severe clinical course of the disease [2, 3]. Virus-related cardiovascular complications, such as myocardial injury, cardiac arrhythmia and thromboembolic events are a frequent finding in patients with COVID-19 [4–6]. In addition, treatment of cardiac patients is further hampered by a significant reduction in diagnostic and therapeutic strategies during the peaks of the pandemic [7–9]. Regarding the substantial impact on cardiovascular medicine, this review focuses on national and international experience with cardiac complications in COVID-19 patients and pandemic-related collateral damage.

Pathogenesis and clinical course

SARS-CoV-2 consists of four structural proteins and a positive-sense, single-stranded RNA with an approximate length of 30 kb [10, 11]. The structural pro-

Table 1 Direct cardiovascular complications and respective incidence rates associated with COVID-19

Incidence rate of cardiovascular complications (%)
Arterial thrombotic events 0.9–1.1 [28, 29]
Venous thrombotic events 6–30 [4, 37–39]
Myocardial inflammation 30–60 [50, 51]
Cardiac arrhythmia 1–17 [54, 56]

teins of the virus form a typical crown-like morphology with spike proteins on its surface [11]. The virus enters the host cells via binding of the spike proteins to the ACE-2 (Angiotensin-converting enzyme 2) receptor, a membrane protein with a particularly high expression on the surface of alveolar epithelial type II cells in the human respiratory tract, causing the typical respiratory symptoms [12, 13]. In the early phase of the pandemic, concerns about the safety of treatment with ACE inhibitors in COVID-19 patients were raised due an upregulation of the ACE-2 receptor [14]; however, several studies and randomized control trials demonstrated that ACE inhibitors can be safely continued despite a SARS-CoV-2 infection [15–18].

The clinical course of COVID-19 varies significantly with many patients experiencing no or only mild symptoms, including fever, fatigue, dry cough and gastrointestinal symptoms [13, 19]. Nevertheless, a substantial number of COVID-19 patients are affected by a more severe clinical course with viral pneumonia and acute respiratory distress syndrome [19]. Notably, infection with SARS-CoV-2 often triggers an amplified inflammatory response with excessive cytokine release, platelet hyperactivity, endothelial dysfunction and systemic inflammation [20–23]. This hyperinflammatory response may provide a potential explanation for the high incidence rate of cardiovascular complications in patients with COVID-19 (Table 1; Fig. 1; [20]).

In addition, SARS-CoV-2 shows a propensity to genetic variations, leading to new variants that might differ in clinical presentation and characteristics [24]. In contrast to the previous year of the pandemic, the latest wave of infections in Europe is mainly driven by the emergence of the B.1.617.2 variant of the SARS-CoV-2 virus, also referred to as delta variant [24]. Data from the European Center for Disease Prevention and Control show that B.1.617.2 accounted for more than 65% of all cases across Europe in the calendar week 28 of July 2021 [24]. The delta variant is associated with a higher transmissibility and might influence the effectiveness of vaccination [25].

The rapid emergence of new variants with a potentially higher risk for an aggravated course underlines the dynamic nature of the pandemic.

Virus-related thromboembolic complications

Thromboembolic events are a frequent complication in COVID-19 patients and contribute to increased morbidity and mortality [20]. Several studies demonstrated the high incidence of thromboembolism that affects both the arterial and the venous system [4, 26, 27]. A multinational observational cohort study of more than 14,000 patients reported that 1.1% of COVID-19 patients presented with acute ischemic stroke during initial hospital admission [28]. Similarly, a stroke rate of 0.9% was reported in a cohort study from New York [29] and COVID-19 was demonstrated to be an independent risk factor for the occurrence of ischemic stroke, with a significantly higher risk in patients with a severe clinical course [30, 31]. Of note, patients with COVID-19 appear to have an increased risk for cryptogenic and large vessel stroke [29, 32]. Patients presenting with ST elevation myocardial infarction (STEMI) and concurrent COVID-19 infection face an increased risk for a poor outcome [33, 34]. Several studies reported that STEMI patients with a concomitant SARS-CoV-2 infection carry a higher thrombus burden and an increased risk of stent thrombosis [33, 34]; however, it remains controversial if SARS-CoV2 can trigger type 1 myocardial infarction itself, potentially via cytokine-related plaque instability [35, 36].

Venous thrombotic events and pulmonary embolism frequently occur in patients with COVID-19 [37–39]. In a Dutch cohort of 184 critically ill patients, the incidence of venous thrombotic complications was 27% despite routine thromboprophylaxis with low molecular-weight heparin (LMWH) [4]. A French multicenter cohort study demonstrated an incidence rate of pulmonary embolism of 8.3% in 1240 consecutive COVID-19 patients, as confirmed with computed tomography pulmonary angiography [40]. As evidence of the activated coagulation system, several studies reported elevated plasma levels of D-dimer in a significant proportion of COVID-19 patients, associated with an adverse outcome [41, 42]. The high rates of thrombotic events make effective antithrombotic treatment essential in the management of COVID-19 patients. Hence, routine thromboprophylaxis with standard-dose LMWH should be established in all hospitalized patients [5, 43–45]. Selected high-risk patients may benefit from an intensified strategy with intermediate-dose or therapeutic-dose administration of LMWH [5, 43], although the evidence for such dosage is still limited [46].

Virus-related myocarditis

Acute myocarditis related to COVID-19 was reported by several case series and smaller studies [47, 48]. In an initial observational study from Wuhan, China, fulminant myocarditis was suspected as the immediate cause of death in 7% of all patients [49]. A prospective

trial performed elective cardiac magnetic resonance imaging in 100 recently recovered COVID-19 patients and reported that 60 patients showed elevated T1 and T2 times, suggestive of myocardial inflammation with late gadolinium enhancement detected in 32 patients [50]. Endomyocardial biopsy was performed in patients with severe findings and showed diffuse active lymphocytic inflammation [50]. Similar findings were reported in a retrospective cohort study of patients with previous SARS-CoV-2 infection who underwent cardiac magnetic resonance imaging, demonstrating that 31% of these patients had significant late gadolinium enhancement [51]. A prospective multicenter study in a cohort of 148 patients with a severe clinical course of COVID-19 detected myocarditis-like scars in 39 (26%) patients via cardiac magnetic resonance imaging [52]. On the contrary, Joy et al. investigated cardiovascular changes in a cohort of 74 patients with a mild clinical course of COVID-19 compared with 75 seronegative control patients 6 months after infection [53]. Thorough analysis of cardiovascular biomarkers and cardiac magnetic resonance imaging did not reveal any long-term cardiovascular abnormalities in COVID-19 patients with only mild symptoms [53].

This data might indicate that SARS-CoV-2 infection frequently causes extensive myocardial inflammation, which may be dependent on disease severity. Potential long-term cardiac sequelae of COVID-19 in this respect still need to be investigated.

Virus-related cardiac arrhythmia

Cardiac rhythm disorders are frequently reported in COVID-19 patients with higher incidence rates among patients with elevated troponin levels or patients on an intensive care unit [54, 55]. Guo et al. reported in a retrospective cohort study that patients with elevated troponin T levels had a significantly higher incidence rate of ventricular arrhythmia compared to patients with normal troponin levels (17.3% vs. 1.5%, $p < 0.001$) [54]. Data from an American registry of consecutive COVID-19 cases reported an incidence rate of malignant ventricular arrhythmia of 11% in patients with a severe clinical course [56]. A meta-analysis of 17 observational cohort studies found an incidence rate of 10.4% of cardiac arrhythmia in COVID-19 patients, although the type of arrhythmia was not clearly defined in this analysis [57]. The propensity for the occurrence of potentially life-threatening ventricular arrhythmia may be the consequence of several contributing factors. In addition to myocardial injury, COVID-19 patients frequently develop metabolic disorders and electrolyte disorders on top of the hyperinflammatory state, creating a milieu that may favor the occurrence of cardiac arrhythmia [56, 58]. It has to be stressed that several drugs initially used to treat COVID-19 have proarrhythmic potential, e.g. hydroxychloroquine and azithromcycin [59, 60]. Although it might pose a logistic challenge in routine clinical practice, selected inpatients might benefit from continuous rhythm monitoring.

Takotsubo cardiomyopathy and COVID-19

In the COVID-19 era, governments worldwide were repeatedly forced to impose drastic public health measures to control and reduce transmission rates of SARS-CoV-2. Strict social distancing rules, self-isolation, quarantine, economic and social stress, in addition to fear of virus infection, exerted significant psychosocial distress on broad parts of the population [61, 62]. Emotional and physical distress are common triggers of the takotsubo syndrome, referred to as stress cardiomyopathy [63]. During the COVID-19 pandemic, a significant increase in the incidence rate of takotsubo syndrome was found [64]. Jabri et al. reported in a North American cohort that the incidence rate of takotsubo syndrome was 4.5 times higher during the COVID-19 pandemic compared to corresponding time frames of prepandemic years [65]. Interestingly, the vast majority of patients presenting with takotsubo syndrome in this study tested negative for SARS-CoV-2, potentially associated with an increased level of stress in the general population [65].

Indirect consequences of the pandemic—Reduction in interventional procedures

Several studies demonstrated that patients with a history of cardiovascular comorbidities have a higher risk for an aggravated clinical course of COVID-19 [41, 42, 54, 66].

In addition to the described direct cardiovascular complications induced by a COVID-19, the pandemic might have several indirect consequences due to a pandemic-related reduction in diagnostic and therapeutic strategies for patients with cardiovascular disease ([67]; Fig. 1). National healthcare systems in several countries had to relocate resources to cope with the high numbers of infected patients [68, 69]. Consequently, a substantial decrease in elective cardiac procedures was observed during the peaks of the COVID-19 pandemic, with significantly lower numbers of patients undergoing routine coronary angiography, pacemaker implantation or cardiac surgery ([9, 70, 71]; Fig. 1). Importantly, the numbers of acute procedures showed a comparable decline [7, 72–74]. An Italian study from 15 cardiac centers reported a reduction of 30% in patients admitted with acute coronary syndrome in February and March 2020, compared to the previous year's respective period [7]. Data from a French registry of 21 participating centers showed a reduction of 24% in hospital admissions for STEMI during the first lockdown, irrespective of the regional prevalence of COVID-19 [72]. Similar numbers were reported in studies from the USA and England [8, 73, 75, 76]. Recent data from Austria have shown that the

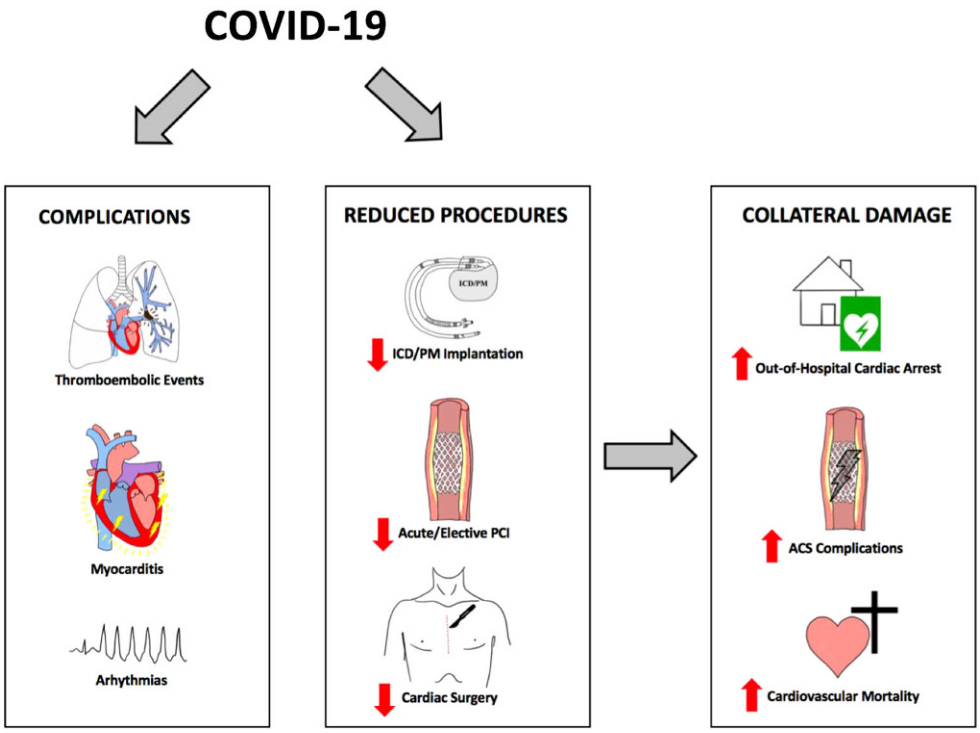

Fig. 1 Direct cardiovascular complications of COVID-19 and indirect collateral damage during the pandemic. *ACS* acute coronary syndrome, *ICD* implantable cardioverter defibrillator, *PM* pacemaker, *PCI* percutaneous coronary intervention

numbers of interventional cardiac procedures were significantly lower in the whole year of 2020 compared to the previous 12 months of 2019 [77]. While a significant reduction of 8% in elective percutaneous coronary interventions (PCI) was observed, the rate of acute PCI showed an even greater decline of 12% [77]. The number of cardiac device implantations and cardiac surgeries were also significantly affected by the pandemic-related lockdown measures [70, 78]. A nationwide analysis from England reported a substantial decline of 44% in pacemaker implantation and of 45% in implantable cardioverter defibrillator implantations during the first wave of the pandemic [78]. Patients admitted for coronary artery bypass craft surgery were markedly reduced by 64% and for surgical aortic valve replacement by 41% compared with the respective period in 2019 [78]. Similar numbers were reported from an Italian multicenter analysis and an international quantitative survey of 60 cardiac surgery centers [70, 79].

Pandemic-related cardiac collateral damage

Reduced capacities for cardiac patients and interventional procedures may have led to significant collateral damage (Fig. 1). An Italian multicenter study reported a threefold increase in STEMI case fatality rate (risk ratio, RR = 3.3, $p < 0.001$) and a substantial increase in complications (RR = 1.8, $p = 0.009$) during the COVID-19 pandemic [80]. These complications included cardiac rupture, ventricular septal defect and severe mitral regurgitation, which may be attributed to prolonged patient delay due to neglected symptoms [80]. Accordingly, the delay from symptom onset to wire-crossing was substantially increased by 39.2% compared to the previous year's respective period [80]. In addition, a profound impact on out-of-hospital cardiac arrest was observed [81]. In the region of Lombardy, Italy, a 58% point increase in out-of-hospital cardiac arrests during the first peak of the pandemic compared to the same period of the previous year was noted [82]. Bystander cardiopulmonary resuscitation was performed significantly less often [82]. Likewise, an analysis from the Paris metropolitan area reported a transient two-times increased incidence rate of out-of-hospital cardiac arrest in the period from March to April 2020 [83]. Furthermore, several studies found a significant decline in admission rates for patients with acute heart failure during the peaks of the pandemic [84, 85]. Patients presenting with worsening or new onset heart failure were in aggravated clinical conditions and had more severe symptoms [84]. Data from England and Germany suggested an increased mortality in heart failure patients during the pandemic [86, 87], although these findings were not confirmed in a recent study from Denmark [88]. Importantly, a potential undertreatment of patients with heart failure during the pandemic may influence long-term prognosis of these patients [89]. Overall, an increased cardiovascular mortality in the COVID-19 era was observed in several studies. Wu et al. reported in a national cohort analysis of England and Wales a proportional increase in cardiovascular mortality of 8% compared with the average of the previous years [90]. An excess in cardiovascular death was also found in studies from the USA and Brazil [91, 92]; how-

ever, a recent analysis from Danish nationwide registries did not identify an increased mortality of patients with established cardiovascular diseases during the pandemic [93]. In this context, it needs to be acknowledged that although increasing evidence for a profound pandemic-related impact on cardiovascular care is available, these data were mostly generated from observational studies [94]. Jung et al. demonstrated in a systematic evaluation that COVID-19 clinical research has lower methodological quality than comparable control studies and should be interpreted with appropriate care [94].

Contributors and implications of reduced capacities for cardiac care

The substantial decrease in hospital admissions and interventional cardiac procedures may have several causes. During the peaks of the pandemic, strict social distancing rules were imposed, avoidance of personal contact was encouraged and the risks of COVID-19 were broadly propagated through public media and the political discourse. Potentially, many patients opted to avoid hospitals and emergency services out of fear of contagion. Even patients with acute medical conditions, including typical signs of an ACS may try to endure symptoms for as long as possible before seeking adequate medical attention [95]. Such changes in patients' behavior led to a significant increase in patient delay and time to wire-crossing in STEMI patients [80, 95]. In addition, relocation of resources to deal with the high number of infected patients may have contributed to the declined numbers of cardiac procedures during the COVID-19 pandemic. Under the continuous pressure of the pandemic, healthcare providers were obliged to establish specialized COVID-19 wards on normal care and intensive care units. Resources from wards of cardiology departments were not excluded from such relocations, as the limited resources of bed capacities and medical staff were partly redirected from the treatment of cardiac patients to the high numbers of COVID-19 patients. As a consequence of these relocations, elective, non-emergency cardiac procedures had to be postponed during the peaks of the pandemic, which led to significantly lower numbers of interventional procedures [70, 71, 77].

Regarding the significant impact of the pandemic on cardiovascular treatment, countermeasures should be considered [96, 97]. Maintenance of well-functioning cardiac care and specialized tertiary hospitals is of utmost importance, especially in times of a global pandemic. Considering the importance of timely primary PCI in the setting of STEMI, patients need to be adequately educated and encouraged to immediately seek medical attention if symptoms suggestive of an ACS are present [98, 99]. It should be emphasized that patients may not avoid contacting emergency services due to fear of potential nosocomial SARS-CoV-2 infections but rather focus on the importance of timely treatment in cases of an acute coronary event. In this context, maintenance of a well-functioning STEMI network is of great importance. Guideline-compliant, timely interventional treatment of patients with a STEMI or high-risk NSTEMI and continued appropriate treatment on specialized cardiac units should not be compromised despite shortages in personnel or resources. Thus, relocation of resources towards the appropriate care of COVID-19 patients may exclude cardiac departments, which carry the responsibility of continued cardiovascular treatment of a population at risk. Finally, it is of utmost need for governments and healthcare systems to provide public information and reassurance to the people to seek medical attention in case of acute or emergency conditions.

Conclusion

The COVID-19 pandemic poses a severe and persistent challenge to national healthcare systems. Patients with pre-existing heart diseases are a vulnerable patient group that may face both direct and indirect consequences of the COVID-19 pandemic. Cardiovascular complications occur frequently and aggravate the clinical course of the disease. While the high numbers of infected patients repeatedly forced healthcare systems to relocate the limited resources towards an adequate treatment of COVID-19 patients, appropriate high-quality care for patients with cardiovascular disease needs to be maintained to avoid collateral damage to this patient group.

Funding The authors report no specific funding for this research article.

Conflict of interest A.L. Burger, C.C. Kaufmann, B. Jäger, E. Pogran, A. Ahmed, J. Wojta, S. Farhan and K. Huber declare that they have no competing interests.

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