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CARDIAC NUCLEAR IMAGING (A. CUOCOLO AND M. PETRETTA, SECTION EDITORS)

Cardiac Imaging on COVID-19 Pandemic Era: the Stand, The Lost, and Found

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Abstract

Purpose of Review The present review will outline the main effects of COVID-19 pandemic on cardiovascular pathologies, focusing on the role of modern non-invasive cardiac imaging techniques in this setting.

Recent Findings Multimodality cardiac imaging seems particularly suited for the in-depth characterization of patients with COVID-19, allowing the assessment of the variegated impact of the disease on the different aspects of myocardial perfusion, structure, and function.

Summary The infection of SARS-CoV-2, leading to the coronavirus disease-19 (COVID-19), has represented a consistent challenge for the organization of the healthcare systems, associating to a significant increase of the fatality rate of different acute and chronic disease. Moreover, the reallocation of healthcare providers led to a significant reduction of the availability of tests and therapies, with the deferral of non-urgent tests and non-lifesaving procedures.

Keywords Cardiac imaging · COVID-19 · MINOCA · Takotsubo

Introduction

The coronavirus disease-2019 (COVID-19) has rapidly led to the transformation of healthcare delivery worldwide, posing unprecedented burden on the sanitary systems and significant risks on the sanitary staff. This impact has progressively translated into consistent modifications on the diagnostic and management pathways of other acute and chronic disease, also including cardiovascular pathologies [1]. In particular, the reallocation of healthcare providers and sanitary expenditures to SARS-CoV-2 containment has significantly decreased the "level of attentions" on other relevant pathologies leading to potential increase of patients' fatality rate [2]. For example, during the peak of SARS-CoV-2 pandemics admissions for acute myocardial infarction were significantly reduced across Italy (−26% for STEMI and −65% for NSTEMI), with a parallel increase in fatality (risk ratio (RR) = 3.3, 95% CI 1.7–6.6; $P < 0.001$) and complication rates as compared to the previous non-pandemic period (RR = 1.8, 95% CI 1.1–2.8; $P = 0.009$) [3]. Similarly, to reduce the possible sources of contagion, the referral of patients to imaging techniques, as well as to invasive procedures, has been reduced substantially, with a particularly adverse impact in the cardiovascular field, limiting diagnostic capabilities and therapeutic approaches [4–6]. This aspect seems of specific relevance in the setting of coronary artery disease (CAD), where recent guidelines have placed non-invasive imaging at the center of the diagnostic and management algorithms [7]. The present review article will summarize some of the most relevant effects of SARS-CoV-2 on the management of cardiac patients, with specific reference to impact of the disease on the patterns of use of non-invasive imaging modalities.

Imaging Lab in the COVID-19 Era

Apart from its obvious adverse social and global sanitary impact, the SARS-CoV-2 pandemic has also consistently increased the burden on cardiac imaging facilities at large. Among the most relevant challenges generally faced by all cardiac imaging facilities during the pandemic, a consistent

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reduction of staff availability—also due to sickness of the medical and/or technical staff—limited consistently the throughput of the laboratories. Moreover, the risk of periprocedural transmission of SARS-CoV-2 between patients and sanitary personnel triggered a consistent increase of procedural (mainly non imaging) times and a further reduction of the tests performed. For these reasons, it is not surprising that a number of medical societies and agencies issued statements providing a guideline on preventive measures and amendments in everyday clinical practice to be implemented during the pandemic. International imaging societies [8••, 9] tried to summarize how these challenges might be addressed during the peak of the pandemic, giving indications about the prioritization of exams based on the appropriateness of the indications and on patients' clinical condition, aiming at safeguarding both patient and staff.

On a general basis, the consensus is that cardiac imaging should be limited to clinically appropriate indications and only if it is likely to substantially change patient management or be possibly lifesaving. In this context the specific imaging modality to be performed should be selected considering the safety of both patients and staff, possibly limiting the time spent by the same patient into the imaging facility [8••, 9]. Accordingly, in patients with ascertained SARS-CoV-2 infection, urgent exams had to be prioritized and elective evaluations/procedures postponed. For instance, in patients with suspected CAD in whom a rapid "rule in/rule out" of high-risk imaging findings, possibly leading to invasive procedures, should have been favored. In this context, computed tomography coronary angiography (CTCA) may offer specific advantages in a large category of patients with suspected or known CAD and ascertained SARS-CoV-2, possibly avoiding invasive coronary angiography (ICA).

Conversely, indications for stress imaging tests should be generally avoided in patients with acute infection, and elective non-urgent and routine follow-up exams may be postponed or even canceled as the results would be very unlikely to alter short-term patient management in most cases [9].

The "American Society of Nuclear Cardiology" (ASNC) provided a classification of priority for all indications for nuclear cardiology studies, according to the level of urgency and estimated benefit:

- *Priority 1 exams (i.e., "evaluation of ischemia in a moderate to high-risk patient with recent acute coronary syndrome considered for urgent coronary revascularization," "evaluation of suspected prosthetic or device infection with 18F-FDG positron emission tomography (PET)," or "Assessment of left ventricular function with MUGA, as an alternative to echocardiography with short duration of patient-staff interaction"): perform test as scheduled.*
- *Priority 2 (i.e., "preoperative evaluation of myocardial ischemia in patient with intermediate or high cardiovascular risk and poor life expectancy from liver disease without transplantation," or "initial evaluation with 18F-FDG PET in patients with heart block or ventricular tachycardia and suspected cardiac sarcoidosis"): postpone test by 2–4 months.*
- *Priority 3 (i.e., "follow-up evaluation of ischemia in patients with stable CAD when there is no urgent revascularization plan"): postpone test by > 4 months.*

Obviously, any classification of procedures' priority requires clinical judgment and may likely derive from an in-depth discussion with both the patient and the referring provider, as now possibly with the use of tele-medicine that would further reduce length of interaction with the patient and, therefore, the risk of infection transmission.

During the phases of high viral transmission such as in the peak phase of the pandemic nuclear cardiology laboratories should generally limit their activity to "priority 1" studies, postponing any exam that would not result in a clinically relevant treatment or definite short-term benefit for the patient [9].

As the pandemic is further evolving, nuclear cardiology facilities (as well as the other cardiac imaging laboratories) have to keep adapting according to the phase of the curve in order to balance between the safety of patients and healthcare professionals while also providing crucial cardiovascular assessments. The use of e-health and telemedicine will have a great role in the future to minimize the risk of re-scheduling the exams and to increase the collaboration between experts.

Imaging Management: the New Challenges

Starting from the early phases of the pandemics, the "International Atomic Energy Agency" (IAEA, Vienna, Austria) coordinated a worldwide study, named the "IAEA Non-invasive Cardiology Protocols Study of SARS-CoV-2" (INCAPS-COVID) to characterize volumes of procedures from facilities around the world that perform diagnostic cardiovascular imaging and interventional procedures. The main results of the global registry [5], assessing objectively how cardiovascular procedure rates changed during the peak months of the pandemic, showed a consistent decrease in the number of cardiovascular procedures being completed (− 68% in the USA vs − 63% in the other regions; $P = 0.237$). These reductions were highest in regions most affected by the pandemic, greater in outpatient than inpatient facilities (− 12.5%; $P < 0.001$) and for more elective procedures. Moreover, the mean reduction in volumes of procedures during the early phase of the SARS-CoV-2 pandemic was 11.5% greater for facilities reporting staff redeployments than those reporting no redeployments and 9.7% greater for urban centers than for non-urban facilities. While, in general terms, a significant reduction of the imaging exams performed was observed, independently of the modality, providers seemed to be appropriately choosing more single-photon emission computer tomography (SPECT) and PET stress tests for the evaluation of inducible myocardial ischemia (both of which can be performed with pharmacologic stress), as suggested in both the European and American recommendation papers [8••, 9], that saw a 75% and 58% reduction, respectively, in the USA. Accordingly, transesophageal echocardiograms, due to its high risk for aerosolizing SARS-CoV-2 transmission, had some of the highest case reductions (80% in the USA and 73% in non-US facilities), whereas computed tomography angiography (CTA) and transthoracic echocardiography had lower reductions.

Specifically, regarding nuclear cardiac imaging, the challenges presented by the SARS-CoV-2 pandemic have favored innovative changes in cardiovascular procedures that will likely affect future standards. Above all, a wider implementation of the "stress first" (stress only) imaging protocol can be foreseen, reducing imaging time and—as already widely reported and supported by existing Guidelines—radiation dose [10]. Starting from the early days of the pandemics, this protocol has been largely embraced, limiting a 2-day nuclear stress test protocols in cases where higher doses of radioisotope should have been injected (i.e., obese patients).

There are significant concerns about how those procedural reductions may impact overall cardiovascular outcomes [11] and if there are induced consequences of delayed cardiac procedures [6].

In fact, patient and population outcomes related to cardiovascular conditions are linked to early and effective diagnosis and evidence-based treatments, thus underscoring the importance of diagnostic and therapeutic cardiovascular procedures in promoting cardiovascular health [12, 13]. Delay in the delivery of these essential services will affect health outcomes and potentially reverse the declines observed in cardiovascular event rates over the past several decades [14]. However, to date, the magnitude of the worldwide impact of SARS-CoV-2 on cardiovascular procedural volumes and changes in testing patterns and modality utilization have not been quantified.

Imaging in SARS-CoV-2 Disease

From the time of its discovery, multiple possible mechanisms of SARS-CoV-2-related cardiac injury have been reported, including systemic inflammatory response syndrome, possibly leading to the so-called "cytokine storm" also characterized by dysregulated autoimmunity; hypoxia-induced myocardial injury in the presence of advanced acute lung injury; cardiac microvascular damage with vessel; direct viral angiotensin-converting enzyme 2 (ACE-2)-mediated damage; vessel thrombosis due to disease-related systemic coagulopathy [15••, 16].

All this disease mechanisms, either in isolation or combined, have been ultimately associated with the possible occurrence of acute coronary syndromes, myo- or pericarditis, Takotsubo cardiomyopathy, and cardiac dysrhythmia.

Given the possibly heterogeneous clinical presentations that can be encountered, the evaluation of patients with SARS-CoV-2 and either clinical, electrocardiographic, or laboratory signs of cardiac damage may take advantage of the use of non-invasive cardiac imaging modalities for both diagnosis, risk stratification, and ultimately, management. Also, in agreement with the recent ESC guidelines on chronic coronary syndromes, CTCA may be recommended for the assessment of SARS-CoV-2 patients with an intermediate pre-test probability of CAD after clinical evaluation, allowing the rapid "rule in/rule out" of high-risk coronary lesions that would merit consideration for revascularization [7]. More recent advances in CTCA technology have allowed the implementation of post-processing imaging algorithms, based on computational fluid dynamics, that can provide an accurate evaluation of the hemodynamic relevance of a given coronary stenosis that well matches with FFR results, likely avoiding the need of further functional imaging. This aspect is of particular relevance in infected patients, limiting staff exposure and allowing a rapid workflow. In the absence of significant obstructive stenoses, different potential differential diagnoses should be considered.

In patients presenting with cardiac symptoms, myocarditis has progressively become an important differential diagnosis during the SARS-CoV-2 pandemic. While the actual prevalence of (peri)myocarditis in SARS-CoV-2 patients is still unknown, with conflicting results coming from either non-invasive and invasive (pathology) studies, data accumulated in the last months point to a non-negligible prevalence of inflammatory cardiac damage in the setting of SARS-CoV-2, possibly also involving patients with asymptomatic infection. Clinical manifestations of SARS-CoV-2-related myocarditis may range from asymptomatic presentations to cardiogenic shock, pointing to the extreme heterogeneity of the virus-host interaction.

SARS-CoV-2-related myocarditis has been linked to different underlying mechanisms that might explain the pathophysiology of cardiac. In this context, while cardiac imaging may have a limited impact on disease management—given the fact that most patients have concurrent systemic manifestations of the infection that should be primarily addressed—it demonstrates (most of the patients also have multiple organ damage, which deserves global treatment) [17•] relevant diagnostic capabilities, also allowing to monitor the evolution of myocardial (dys)function.

In this regard, although echocardiography remains the first-line imaging test for the evaluation of peri-myocardial structure and function in patients with suspected or known cardiac inflammatory disease, cardiac magnetic resonance (CMR) maintains insuperable diagnostic capabilities, due to the ability to provide non-invasive tissue characterization. Specifically, CMR imaging may show either focal or diffuse myocardial oedema causing pseudo wall hypertrophy as well as non-infarct patterns by the use of late gadolinium enhancement and different T1 and T2 sequences [18] (Fig. 1).

It should be noted that pericarditis may co-exist with myocarditis—needing special consideration for differential treatment—although the two conditions may present separately.

Possibly further complicating the spectrum of SARS-CoV-2-related cardiac manifestations, it has been consistently reported that also "myocardial infarctions with non-obstructed coronary arteries" (MINOCA) may be quite frequent, pointing on the need of close clinical monitoring of infected patients presenting with cardiac symptoms [19, 20].

ECG monitoring is recommended in patients with MINOCA, taking into account the possible risk of ventricular arrhythmias. In the setting of a MINOCA, myocardial PET imaging may have a role, due to the chance of non-invasive quantification of myocardial blood flow (MBF) and flow reserve at rest and during pharmacologically induced maximal hyperemia, this being the reference standard for the diagnosis of coronary microvascular dysfunction as the cause of myocardial injury [21, 22].

PET has been largely validated and compared to other invasive and non-invasive tests for ischemic burden assessment both in patients with CAD or non-ischemic cardiomyopathies. More recently, quantitative MBF assessment has been also validated by dedicated cardiac cameras equipped with Cadmium-Zinc-Telluride (CZT) detectors. Specifically, estimates of myocardial perfusion parameters derived through dynamic CZT imaging have been shown to match the outputs of both non-invasive and invasive gold-standards (i.e., PET and FFR, respectively), providing excellent

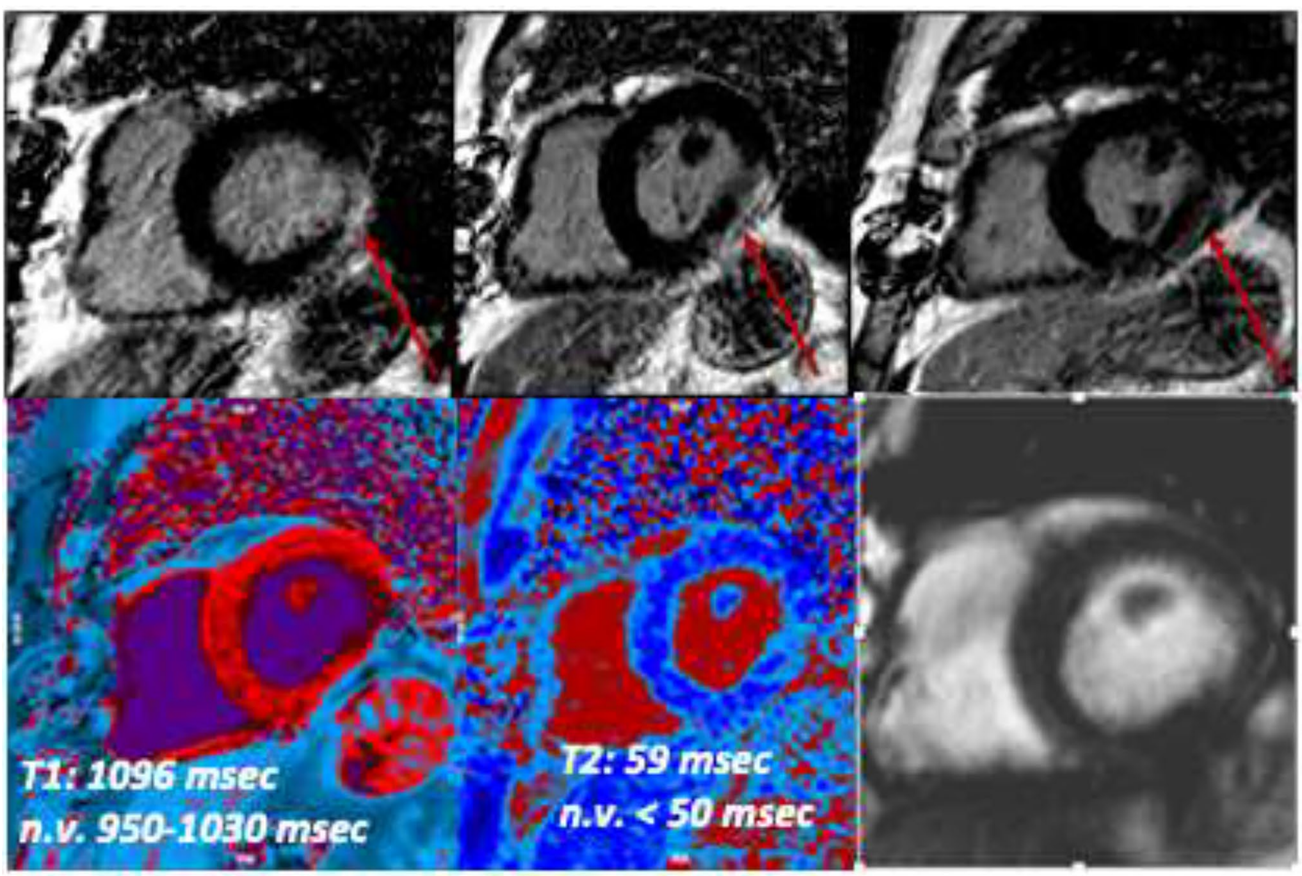

Fig. 1 Typical cardiovascular magnetic resonance (CMR) findings of myocarditis. LGE of the subepicardial region (*red arrows*) of the ventricles represents a sign of myocardial fibrosis or scarring. The abnormal values of T1 and T2 mapping confirm the LGE sign of myocarditis. Courtesy of *Prof. Marco Francone MD*, *Humanitas Research Hospital and University, Milan (Italy)*

diagnostic and prognostic information despite a contained imaging and computation time [23].

The occurrence of Takotsubo cardiomyopathy has been also increasingly reported in the setting of SARS-CoV-2. While trans-thoracic echocardiography is the first-choice technique for both the initial characterization and immediate follow-up of patients with Takotsubo cardiomyopathy, CMR may be most appropriate for a differential diagnosis with MINOCA.

In Takotsubo cardiomyopathy, nuclear cardiac imaging may play an important role for the estimation of patients' arrhythmic risk by the evaluation of the presence and the extent of sympathetic innervation injury, a known powerful predictor of adverse cardiac events, including malignant ventricular arrhythmias [24].

Finally, in the absence of another firm diagnosis, contrast-enhanced computed tomography (CT) of the thorax should be considered in all SARS-CoV-2 patients with chest pain, in order to assess the presence of either a pulmonary embolism or an acute aortic syndrome, the former disease particularly prevalent in patients with SARS-CoV-2 pneumonia, systemic inflammatory response, and virus-related coagulopathy.

Conclusions

COVID-19 pandemic has posed novel challenges to the healthcare systems worldwide, leading to an increase of the fatality rate of major pathologies. In particular, the event rate of acute coronary syndromes has increased substantially, likely because of a multiplicity of factors, also including delayed patient' referral due to the fear of contagion. A marked reduction of worldwide cardiovascular testing has been also witnessed, with guidelines generally recommending the deferral of non-urgent cases and of stress tests at large. On the other hand, the direct adverse impact of COVID-19 on the cardiovascular system points to the need of a redefinition of the use of cardiac imaging in the affected patients, both for disease diagnosis and risk stratification. In this setting, multimodality cardiac imaging seems particularly suited for the in-depth characterization of patients with COVID-19, allowing the assessment of the variegated impact of the disease on the different aspects of myocardial perfusion, structure, and function.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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