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ACUTE CORONARY SYNDROMES AND COVID-19: A LITERATURE REVIEW

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Abstract: The coronavirus pandemic has had an unprecedented impact on healthcare systems, including acute cardiology services. COVID-19 directly leads to cardiac complications in patients with underlying heart disease or cardiac risk factors. As future waves of the coronavirus are anticipated, it is prescient to review its impact on the delivery of cardiovascular care, in particular the treatment of acute coronary syndromes. A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); Base; Web of Science, Google Scholar. Conference abstracts/papers have been deleted from Embase. The search strategy was designed to capture the theme in current reviews of COVID-19 Acute Coronary Syndromes. Immediate and early revascularization, with adequate personal protective equipment, remains the standard care approach for patients with acute coronary syndrome in the COVID-19 era. Adapting cardiac services to ensure continuity of care for these patients, even in the context of a new wave of COVID-19, is essential to minimize preventable cardiovascular death.
Keywords: COVID-19; acute coronary syndrome.

INTRODUCTION

The coronavirus (COVID-19) pandemic has had an unprecedented impact on healthcare systems, including acute cardiology services (RASHID et al. 2020). COVID-19 directly leads to cardiac complications in patients with underlying heart disease or cardiac risk factors. COVID-19 indirectly impacts patients through the necessary shift in healthcare resource allocation and the need for social distancing. A reduction in health-seeking behavior, a reduction in calls for cardiac emergencies, and a reduction in traditional chronic care will have implications that go beyond the infectious reach of the

virus. Therefore, cardiovascular care during the pandemic must remain a priority to mitigate the significant morbidity and mortality from both the direct and indirect effects of COVID-19 (PONTONE et al. 2020). As future waves of the coronavirus are anticipated, it is prescient to review its impact on the delivery of cardiovascular care, in particular the treatment of acute coronary syndromes (ACS).

MATERIAL AND METHODS

A review of the current literature was carried out. The following databases were consulted: MEDLINE (PubMed); Base; Web of Science, Google Scholar. Conference abstracts/papers have been deleted from Embase. No other limits were applied. All retrieved records were organized using Endnote citation management software version 20. To remove duplicates, literature review citation screening and review software was used.

The search strategy was designed to capture the theme in current reviews of COVID-19 Acute Coronary Syndromes. Searches were complemented by hand searching and retrieving any additional articles that met the eligibility criteria that were cited in our reference lists.

DEVELOPMENT

CARDIOVASCULAR CONCERNS IN COVID-19

Early reports suggested a strong relationship between traditional cardiovascular risk factors and poor COVID-19 outcomes (SINGH et al. 2020; VECCHIO et al. 2020). COVID-19-related myocardial injury is evident post mortem (SINGH et al. 2020). Those with critical illness demonstrate elevated levels of troponin and B-type natriuretic peptide (BNP) and increasing levels correlate with worse clinical outcomes (SCHIAVONE et al. 2020).

Myocardial injury mechanisms remain poorly understood, but candidates may involve ACE2 expression in the myocardium and coronary vessels, triggering local inflammation, hypercoagulopathy, and thrombosis. Coronary thrombosis will cause ACS and localized ischemia in the form of type I myocardial infarction (MI) (MOUNTANTONAKIS et al. 2020). Ischemia can also result from respiratory failure and hypoxia; in the context of underlying coronary disease, increased troponin may reflect a type II AMI due to supply / demand mismatch (MATSUSHITA et al. 2021). Pulmonary emboli may also occur, leading to elevated pulmonary pressures with right ventricular distention (GUIMARÃES et al. 2020). An immune-mediated inflammatory response appears to lead to secondary myocarditis and contributes to acute heart failure and multiorgan failure (GRIFFIN et al. 2020). Myocarditis in COVID-19 generates marked changes on the ECG with marked and even regional ST elevation ('STEMI'). Furthermore, the sympathetic drive can lead to Takutsubo-type cardiomyopathy or lead to cardiac arrhythmia.

ACUTE CORONARY SYNDROMES

In the pre-COVID-19 era, the diagnosis of ACS was based on classic symptoms of chest discomfort (often associated autonomic features), electrocardiographic features, and increased cardiac biomarkers (usually troponin). Treatment requires antiplatelet agents (aspirin with a potent $P2Y1_{12}$ antagonist such as clopidogrel, prasugrel, or ticagrelor), injectable anticoagulants (such as fondaparinux), and cardiac demand modification (with beta-blockers) (CHIEFFO et al. 2020). Statins are given early as they can promote plaque stabilization. While initial reports raised concerns about ACE inhibitor and angiotensin receptor use in patients

with COVID-19, age-corrected models did not support this, and ARBs may even have a protective role (ASHRAF et al. 2020).

Those with higher-risk features, such as significant troponin markers, ongoing ECG changes, or high GRACE scores, receive invasive angiography, as revascularization reduces poor outcomes, including reinfarction (BRAITEH et al. 2020). In ST segment elevation myocardial infarction (STEMI), immediate revascularization with primary percutaneous coronary intervention (PCI) is essential. Left untreated, ST-elevation Myocardial Infarction (STEMI) has high mortality and risks of mechanical complications such as mitral regurgitation or ventricular septal defects (CAPACCIONE et al. 2021). The door-to-balloon time must be less than 60 minutes when feasible. Myocardial infarction without ST-segment elevation (NSSTEMI) must undergo angiography within 72 hours, preferably earlier.

All of these factors hold true in the COVID-19 era with the additional assessment of infectious status and adequate staff protection. COVID-19 treatment algorithms have incorporated the use of anticoagulants due to thrombotic risk (CHIEFFO et al. 2020). Ischemic events can be reduced by the addition of rivaroxaban 2.5 mg twice daily and ongoing studies are evaluating this in the era of COVID-19.

While chest pain is common in COVID-19, the symptoms of true MI remain distinct and detectable on history taking. The key issue is to distinguish these type I MI events from troponin elevation due to arrhythmia, heart failure, myocarditis, pericarditis, or systemic disease (type II MI) (COURAND et al. 2020). Clinical evaluation, serial ECG and troponin measurement are fundamental for the diagnosis. In the context of COVID-19, conservative management may be appropriate for non-true ACS.

Point of care echocardiography can support decision-making: the presence of regional wall motion changes would suggest typical ACS. As echocardiography is an intimate examination with a prolonged period of contact between the patient and the healthcare professional, there is an increased risk of viral transmission and the use of full personal protective equipment (PPE) is recommended. Focused scans with limited views to answer the question are appropriate. Patients must wear masks during the scan and during their evaluation and treatment.

REPERFUSION FOR STEMI

In STEMI, rapid mechanical reperfusion via primary percutaneous coronary intervention (PPCI) is the preferred treatment option (COURAND et al. 2020). The National Health Service and the British Cardiovascular Intervention Society have reiterated that ICPP remains the treatment of choice for STEMI in the COVID-19 era (GRIFFIN et al. 2020). In the UK, most cardiac networks have STEMI diagnosed by ambulance services, and patients are taken directly to designated cardiac catheter labs. Occasionally, patients may need acute transfer from district general hospitals to central hospitals if the first hospital cannot provide revascularization in a timely manner. Usually, intensive care ambulances are needed for this.

As there is an asymptomatic period when infected patients are shedding the virus, those presenting as emergency STEMI can lead to viral transmission to first responders and those performing PCI. COVID-19 diagnostic tools are not yet fast enough to allow pre-emergency ICPP screening for STEMI, and while chest CT screening is useful in more elective settings, it is impractical in a STEMI setting. As ICPP may involve cardiac arrest, a recognized 'aerosol-generating procedure', it is agreed that full PPE is recommended for

all those undergoing ICPP (DE HAVENON et al. 2020; GUIMARÃES et al. 2020). Services must consider protecting staff members most at risk of COVID-19: those with lung disease or those over the age of 65 transferred to activities not adequately patient-focused.

ICPP must be performed with reperfusion within 120 minutes of symptom onset and within 60 minutes of arrival at a center capable of ICPP (GUIMARÃES et al. 2020). Radial access is preferred to facilitate early patient ambulation. Observational data suggest that those with COVID-19 have a higher thrombus burden: rates of multivessel thrombosis and stent thrombosis are higher (JENAB et al. 2020). Higher rates of aspiration thrombectomy and greater need for GPIIb/IIIa and higher doses of intraprocedural heparin are reported (LANG et al. 2020). Prolonged hospitalization and higher mortality are observed in those with COVID-19 and STEMI (MATSUSHITA et al. 2021; LI et al. 2021)

A dedicated catheter laboratory is recommended and all possible equipment must be available to limit the need for a team to fetch equipment and potentially spread the virus. A designated area for putting on and taking off PPE is essential; employees must observe each other to support this process. All team members must have sufficient PPE with a mask, lab coat, goggles and/or FF2 or FFP3 visor. As PPE remains scarce, some may choose to limit the use of PPE to carriers only. However, in the event of cardiac arrest, team members will need to leave the cardiac catheter lab to put on PPE prior to exposure to cardiopulmonary resuscitation (CPR) maneuvers.

Negative pressure installations have been recommended to minimize the spread of the virus, but few have this capability. The alternative is to deep clean after each box. In case of multiple STEMI patients arriving at the same time, a risk assessment must be carried out and, if delays are unavoidable, thrombolysis must be considered.

In those who develop cardiogenic shock in the context of COVID-19 infection, futility must be considered. However, as decision-making in acute situations can be challenging, all available supportive therapies must be used when appropriate.

THROMBOLYSIS FOR STEMI

Although ICPP remains the treatment of choice for STEMI, the number of COVID-19 cases in Wuhan and Lombardy has raised enough concerns that thrombolysis must be considered in certain circumstances (RASHID et al. 2020; MOUNTANTONAKIS et al. 2020; PONTONE et al. 2020; PONTONE et al. al. 2020).

Under normal circumstances, transfer to ICPP centers is effective and safe. However, during the peak of COVID-19, hospital transfers were affected and for unwell COVID-19 patients who are actively shedding virus, they are potentially dangerous. Additionally, critically ill patients requiring non-invasive ventilation are difficult to safely transfer with aerosolized secretions that pose a threat to staff. Intubated patients have closed circuits that reduce the risk of transmission, but these patients remain a challenge to transfer in a timely manner. Patients in intensive care units (ICU) in district generals without acute primary angioplasty services will be at a disadvantage as acute transfer to local PCI centers will be delayed.

In these situations, thrombolysis must be considered early and administered immediately in the absence of contraindications; the highest value is within 1 hour of pain onset. Fibrin-specific agents such as alteplase and tenectaplase can be administered easily; the latter is preferable as a single bolus reduces the need for close nursing contact.

The use of thrombolysis remains

controversial with concerns about bleeding risks in the context of possible COVID-19 myocarditis. Furthermore, a quarter of patients will not reperfuse and still require facilitated PCI (ROWLAND et al. 2020). However, despite these concerns, thrombolysis is used for STEMI worldwide and has been used successfully in patients with COVID-19 in China (SCHIAVONE et al. 2020). Although ICPP has a clear advantage in reducing the risk of bleeding and increasing the likelihood of reperfusion, the efficacy balance between thrombolysis and ICPP is closer to the balance when ICPP is delayed. The strategic reperfusion study shortly after myocardial infarction (STREAM) demonstrated that even a single hour delay meant that there was no significant difference in major events after being randomized to thrombolysis or ICPP (SINGH et al. 2020).

Patients must be urgently discussed with a senior cardiologist and an interventional cardiologist. Fast communication is essential and may need to be fully remote to facilitate speed. Documentation must reflect on why thrombolysis is used and the system restrictions that mandate it. Initial decisions must be documented for subsequent treatment for those patients in whom the ST segments do not resolve sufficiently. A cardiac catheter laboratory must be activated and steps taken for a safe transfer. Patients who achieve reperfusion must be considered for invasive stabilization angiography.

UNIQUE ISSUES RELATED TO ACS IN THE COVID-19 ERA

STEMI

Unwell patients with COVID-19 manifested severe ST elevation, but unobstructed coronary arteries were found on invasive angiography (TAN et al. 2020). The mechanism remains unclear, but is attributed to myocarditis or a Takutsubo-type response to intense inflammation. As the number of COVID-19 cases increased in Wuhan and Lombardy, there were concerns that ICPP services would be overwhelmed by similar patients and expose them to the risks of unnecessary invasive procedures (BRAITEH et al. 2020; CAPACCIONE et al. 2021). However, this has been less evident in the UK. Echocardiography can help support the diagnosis of global myocarditis, but coronary angiography is still advocated to avoid missing a true coronary occlusion (GUIMARÃES et al. 2020).

LATE SERVICE

As the pandemic progressed, a global reduction in CHA admissions was observed (ASHRAF et al. 2020). This is perhaps in response to strong government messages to 'stay at home'. Interestingly, patients avoided hospitals despite significant cardiac symptoms. Patients may fear contracting the virus or wish to avoid overwhelming medical services. Referents in primary or intermediate care settings may misinterpret chest pain as part of COVID-19. Those in smaller district hospitals may not be able to transfer patients to catheter laboratory centers due to saturation of emergency services (TOUŠEK et al. 2021). Globally, a 20% to 40% reduction in STEMI presentations has been reported; greater reductions in NSTEMI are observed (ROFFI et al. 2020; TAM et al. 2020). Participants experienced significantly longer door-to-balloon times, with longer assessment times in emergency rooms, longer times for staff to prepare PPE, and potentially longer procedure times due to clot burden, disease complexity, or need for respiratory support (ROFFI et al. 2020; CHOR et al. 2020).

Late presentations for STEMI have increased and may have a large thrombotic burden with reperfusion failure despite PCI (ROFFI et al. 2020). Mechanical complications

such as septal defects and ventricular rupture have been reported. It is expected that the incidence of heart failure may increase due to this late presentation with ACS. UK national PCI and MI registries are being used to study the pattern of admissions by ACS since the start of the pandemic (VECCHIO et al. 2020).

NEW PATHS AND NEW WAYS OF WORKING

Significant changes in work patterns meant that new avenues of care were instituted. Some of them may have value beyond the pandemic. Paths must be modified according to locally available resources.

MINIMIZED STAY TIME

Immediate treatment and minimization of tests that are unlikely to change short-term clinical decisions must help minimize the patient's length of stay. This is important to reduce the likelihood that patients will acquire de novo coronavirus infection from other patients. In efficient healthcare systems with early reperfusion, it must be feasible for uncomplicated AMI to be discharged within 24 hours of admission. Immediate review in emergency departments with same-day angiography must be considered when possible. As elective care has been reduced, catheter labs have the ability to turn around quickly, and radial access allows for early discharge. Bedside point-of-care echocardiography can provide LV assessment. A short period of rhythm monitoring is appropriate in low-risk patients with uncomplicated PCI. Tests such as positron emission tomography (PET), myocardial perfusion imaging (MIBI) and magnetic resonance imaging (MRI) are less available in the current pandemic. Unless essential for decision-making, it is suggested that these tests be postponed to reduce length of stay.

Low-risk patients with low Global Registry of Acute Coronary Events (GRACE) scores and small elevations in troponin can be stratified and, if appropriate, early urgent angiography can be considered on an outpatient, outpatient basis. Some Trusts have maintained angiographic facilities in 'clean zones', allowing patients to be discharged from emergency departments and appear semi-electively the next day for the invasive procedure, minimizing the hospital stay. Maximal antiplatelet therapy and appropriate counseling is required.

HOSPITALIZATION OF CONTAMINATED PATIENTS

In some cases, hospitalization is unavoidable. Hospitals have developed clearly demarcated 'zones' to reflect the likelihood of viral cross-contamination. Patients with confirmed COVID-19 must be grouped with other carriers of the virus. However, delays in viral diagnosis may apparently mean well, but infected and shedding patients may enter ostensibly "clean" zones.

FUTURE PERSPECTIVES POST-COVID-19

The emergence of a new virus implies decisions that seek to mitigate its pathogenic effects, prevent intense transmissibility and population illness.

The COVID-19 pandemic has generated a rapid set-up of services in hospitals, aided by the reduction of bureaucracy. Acute services have been reconfigured to reduce the spread of the coronavirus by segregating acute assessment areas, wards and catheter labs into "clean" and "dirty" zones. Patients are stratified by likelihood of infection. Upstream smearing and temperature assessment are essential. Unfortunately, keeping sites strictly clean will be difficult in acute care, particularly for STEMI, and PPE must continue to be used when patients are at risk of infection. Faster

and faster swab protocols may facilitate more selective use.

Elective work, which has been delayed by the pandemic, has been restored using enhanced pre-procedure assessment with comprehensive scanning and patient self-isolation prior to elective procedures. The duration of isolation seems to vary between hospitals. Biweekly staff cleaning can help identify illness among staff and reduce the chance of facility closures or patient infection. Outpatient elective surgery has been stratified by urgency and in some places moved to different hospital locations to ensure there is no impact on intensive care services. In the longer term, normal clinical services must return to minimize a growing inequality of service access.

Outpatient flows have benefited from technology adoption. Clinics become remote to reduce patient viral exposure. Phone and video clinics are now fully established and in many cases can replace traditional clinics. In-person consultations can be reserved for specific patients, but must include appropriate PPE and social distancing to reduce the risk of exposure to cardiology patients who are specifically vulnerable to complications. "Virtual" post-infarction cardiac rehabilitation and heart failure clinics have proven to be viable.

In the future, work is needed to anticipate the possibility of new 'waves' of the virus. Cardiologists may need new models of work, going beyond work schedules and may require shift patterns.

FINAL CONSIDERATIONS

Patients with ACS may have coronary disease that is better revascularized by coronary artery bypass grafting. At the start of the pandemic, all elective surgeries were canceled to reduce the impact on intensive care facilities. This has evolved to allow urgent surgery once discussed in a multidisciplinary team meeting (MDT), but in a limited number of centres. MDT must be performed early and preferably daily to minimize uncertainty and length of stay. In patients with COVID-19, there is concern that surgery poses undue risk and harm. In these cases, PCI must be preferred whenever possible. As surgical disease can be complex, additional care and attention will be required when performing PCI, taking into account adjuvant technologies.

ACS management remains a key priority and services must be adaptively configured to respond to the ever-changing demands of the pandemic. Treatment for ACS is well-established, and while an effort must be made to adhere to standard pathways, judicious use of pharmacological and diagnostic adjuncts may allow deviation from these pathways to identify and treat those that are not true ACS and those that are simply unstable to benefit from standard treatment strategies.

Immediate and early revascularization, with adequate personal protective equipment, remains the standard care approach for patients with acute coronary syndrome in the COVID-19 era. The use of risk stratification tools (such as GRACE scores) can help prioritize cases to minimize their hospital stay. Critically unwell patients with ST-elevation myocardial infarction, no catheter laboratory facilities in place, or too unstable for transfer must be considered for thrombolysis and activation of services for facilitated PCI, if needed. Patients with cardiovascular disease are particularly vulnerable during this period, regardless of their infectious status. Adapting cardiac services to ensure continuity of care for these patients, even in the context of a new wave of COVID-19, is essential to minimize preventable cardiovascular death.

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