Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

MAYO CLINIC

COMMENTARY

ST-segment Elevation, Myocardial Injury, and Suspected or Confirmed COVID-19 Patients: Diagnostic and Treatment Uncertainties

Check for updates

Courtney E. Bennett, DO; Nandan S. Anavekar, MD; Rajiv Gulati, MD; Mandeep Singh, MD; Garvan C. Kane, MD, PhD; Yader Sandoval, MD; Thomas A. Foley, MD; Allan S. Jaffe, MD; Gurpreet S. Sandhu, MD, PhD; Malcolm R. Bell, MD; and J. Wells Askew, MD

From the Department of Cardiovascular Medicine (C.E.B., N.S.A., R.G., M.S., G.C.K., Y.S., A.S.J., G.S.S., M.R.B., J.W.A.) and Department of Radiology (N.S.A., T.A.F.), Mayo Clinic, Rochester, MN.

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 and has resulted in a global pandemic with considerable morbidity and mortality.[1-3] Multiple studies have noted both increased susceptibility in patients with underlying cardiovascular disease to COVID-19 and severe cardiovascular sequelae in COVID-19–infected patients, including acute myocardial injury, arrhythmias, and shock.[3,4] In addition, there have been several reports of ST-segment elevation (STE) in patients with COVID-19 who do not have evidence for obstructive coronary artery disease on invasive coronary angiography.[5,6] The effect of "false" catheterization laboratory activation includes multiple inherent risks arising from the following: an invasive arterial procedure and adjunctive antithrombotic administration for these patients; the exposure of personnel during transfers; and possible respiratory failure in patients with COVID-19 and subsequent aerosol-generating procedures during resuscitation and intubation. The downstream effects of inadvertent exposure and contamination may not be trivial and could result in critical isolation of the exposed staff. The potential effects may result in staffing shortages leading to slowed or even closed cardiac catheterization or other cardiac imaging services, especially in smaller facilities. Conversely, it remains critically important to provide timely emergent reperfusion therapy in patients experiencing an acute myocardial infarction (MI) due to acute coronary occlusion.[7] Thus, there is an urgent need for an algorithm that facilitates triage of suspected or proven COVID-19 patients with STE toward initial invasive or noninvasive pathways.

The reported experiences, published and unpublished (correspondence, ad hoc webinars, and social media), from countries in which substantial exposure to COVID-19 has occurred highlight the enormous challenges with regard to the evaluation and treatment of patients with COVID-19 and STE on the electrocardiogram. These experiences emphasize the need for health care facilities to rapidly prepare and configure their own ST-segment elevation myocardial infarction (STEMI) systems of care in anticipation of treating increasing numbers of patients with COVID-19 whose clinical course is complicated by the appearance of STE on their electrocardiogram. It is within this context that we offer this background information and proposal of algorithms for the evaluation and treatment of these patients.

ACUTE MYOCARDIAL INJURY

Acute myocardial injury (rise and/or fall of cardiac troponin [cTn] with at least 1 value >99 percentile upper reference limit)[8] is common in patients with acute respiratory infections and correlated with disease severity.[9-11] Abnormal high-sensitivity cTn

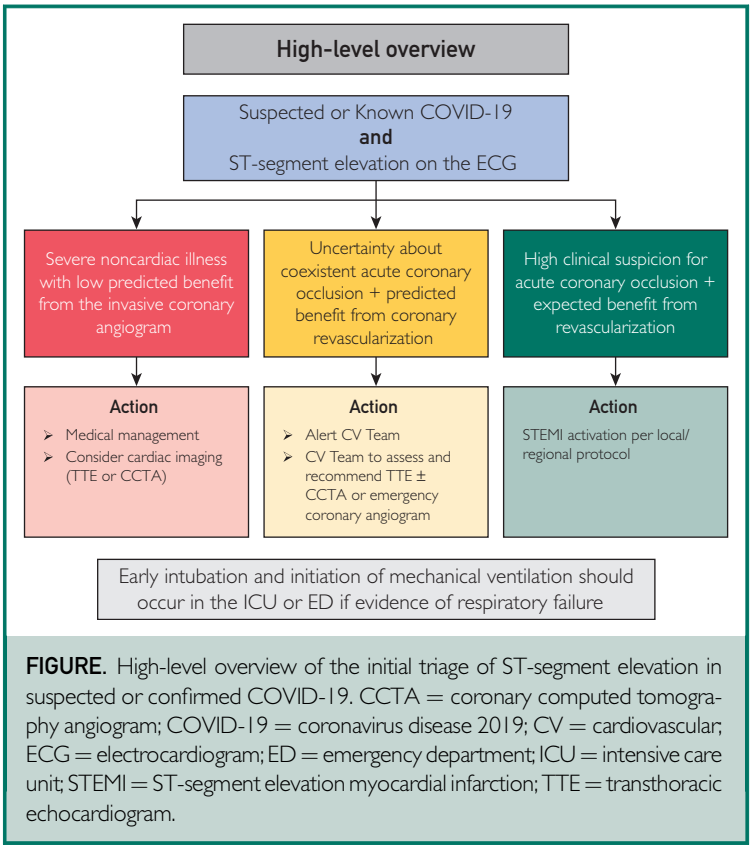

FIGURE. High-level overview of the initial triage of ST-segment elevation in suspected or confirmed COVID-19. CCTA = coronary computed tomography angiogram; COVID-19 = coronavirus disease 2019; CV = cardiovascular; ECG = electrocardiogram; ED = emergency department; ICU = intensive care unit; STEMI = ST-segment elevation myocardial infarction; TTE = transthoracic echocardiogram.

values are common in patients with COVID-19 and are significantly higher in nonsurvivors.[3,12] The mechanisms for these cTn elevations are incompletely understood, but likely reflect underlying cardiac comorbidities and potentially reflect acute myocardial injury due to direct toxic ("noncoronary") myocardial damage, critical illness, cytokine storm, heat shock proteins, or stress cardiomyopathy. All these mechanisms can occur in patients with acute respiratory failure and/or systemic infections because of various etiologies.[8,13] Marked alterations in myocardial oxygen consumption and supply-demand mismatch, with or without bystander concomitant atherosclerotic coronary artery disease, can lead to type 2 MI.[8,13] Type 2 MI is typically treated with noninvasive medical management.[13] However, on occasion, type 1 MI related to atherosclerotic plaque disruption can be triggered by the inflammatory milieu caused by a respiratory infection,[14-16] typically necessitating invasive stabilization. In the absence of STE or hemodynamic instability, many of these events probably can be managed medically. The incidence of acute MI (including MI subtypes) in COVID-19 is unknown, although the sparse electrocardiographic data that are available suggest that acute ischemic events are uncommon. It is critical to understand that increased cTn concentrations are common in patients with acute illnesses such as COVID-19, particularly when using high-sensitivity cTn assays in which modest elevations exist in many adults with comorbidities for varied reasons.[4,8,12] The recent diagnostic guidelines for acute MI emphasize that a significant change in cTn concentrations is insufficient for the diagnosis of MI. The significant change in cTn concentrations must be accompanied by *clinical evidence of overt myocardial ischemia.*[8] The subsequent pathways emphasize the critical importance of clinical assessment of patients presenting with STE and the necessity of establishing clinical evidence of myocardial ischemia before rushing such patients to the catheterization laboratory.

ST-SEGMENT ELEVATION CARE PATHWAYS

The approach to STE in patients with suspected or confirmed COVID-19 can be challenging for the reasons we have described above. ST-segment elevation may occur because of atherothrombotic type 1 or type 2 MI including vasospasm, but recent reports suggest that STE can occur because of COVID-19–related myopericarditis.[6] To facilitate diagnosis and management, we created a multidisciplinary working group of experts in acute cardiac critical care, ischemic heart disease, invasive cardiology, and cardiac imaging to propose an algorithm delineated in the Figure. This algorithm seeks to achieve the following objectives: (1) the accurate identification of patients with type 1 or type 2 MI who would benefit from reperfusion therapy and revascularization, (2) the minimization/avoidance of unnecessary exposure of patients with COVID-19 to invasive care and pharmacological management that may result in

Mayo Clin Proc. ■ June 2020;95(6):1107-1111 ■ https://doi.org/10.1016/j.mayocp.2020.04.005
www.mayoclinicproceedings.org

clinical harm, and (3) the use of a strategy to wisely utilize resources and avoid unnecessary exposure to a potentially fatal infectious agent. The proposed algorithm (Figure) is a basic high-level decision aid for the immediate management of STE in patients with suspected or proven COVID-19. An important aspect of care in managing patients with COVID-19 is to minimize the patient's footprint in the inpatient environment to reduce risks to both the patient and others including health care workers, hospital patients, and physicians. This approach, however, must be balanced against the need for a rapid and precise diagnosis in COVID-19 patients with STE due to an acute MI for timely and appropriate reperfusion therapy including coronary revascularization to be implemented when appropriate. We recommend considering an approach that takes into account severity of illness coupled with risk stratification using cardiac imaging in select cases to assess the potential benefit from coronary revascularization rather than a blanket policy of proceeding with diagnostic catheterization, often triggered by prehospital electrocardiographic testing, for all patients with STE with suspected or known COVID-19. We recognize that strategies will vary depending on the specifics and capabilities/resources at any given institution and may reflect some ethical concerns for the health care staff.

Our current approach in patients with a high suspicion for acute coronary occlusion who are candidates for coronary angiography with an expected benefit from coronary artery revascularization is to continue with the standard prehospital or emergency department (ED)—triggered STEMI activation of the cardiac catheterization laboratory (CCL) for the anticipated primary percutaneous coronary intervention. Protection of the CCL team is of paramount importance, and rigorous COVID-19 CCL protocols should be followed to protect individuals from airborne, droplet, and contact infection sources, given the potential high risk of aerosol-generating procedures.[17] The strategy at our institution is to continue primary percutaneous coronary intervention for most patients, with occasional fibrinolytic therapy as per our normal STE pathways,[18] rather than adopt a strategy of preferential fibrinolytic therapy in patients with suspected or known COVID-19. We recognize that revascularization strategies may evolve on the basis of the COVID-19 effect on the CCL availability. On the other end of the spectrum, there will be patients with COVID-19 with severe respiratory and multisystem organ failure who are less likely to derive substantial benefit from emergent coronary angiography and revascularization because of the potentially higher likelihood of myopericarditis. We acknowledge that it will be difficult not to activate the CCL team in these patients, despite the identification of STE. We recommend a multidisciplinary team review acutely if there is any doubt about the likelihood of type 1 MI. A similar approach should be considered for those with cardiac arrest and/or cardiogenic shock in whom clinical history is ambiguous. There may be uncertainty about the likelihood of acute coronary occlusion in patients with COVID-19 and STE within that spectrum because of any one of the following considerations: (1) the clinical presentation is not consistent with acute ischemic symptoms, (2) the only cardiopulmonary symptom is dyspnea in the setting of a presumptive respiratory infection with or without radiographic findings consistent with COVID-19, or (3) there is a paucity of traditional risk factors for coronary artery disease. In these scenarios, taking additional time to consider the value of upstream (pre-CCL STEMI activation) adjunct cardiac imaging including echocardiography or coronary computed tomography angiography (CCTA) may reduce unnecessary invasive coronary angiography and thus CCL exposure to a highly contagious virus. The selection of the particular imaging modality should be chosen on the basis of patient factors such as age, renal function, body habitus, hemodynamics, and surgical

and/or percutaneous coronary intervention history.

ADJUNCT CARDIAC IMAGING

The decision on using a focused and rapid goal-directed transthoracic echocardiogram and/or CCTA in patients admitted to the ED or intensive care unit (ICU) will be predicated on multiple factors apart from the estimated likelihood of a primary acute ischemic event; these include patient symptoms, hemodynamic stability, availability, and proximity of the imaging studies to the ED, as well as time to image acquisition, study completion, and interpretation.

A goal-directed echocardiogram focusing on left ventricular systolic function and regional wall motion analysis performed in the ED or ICU can be instrumental in the decision of CCL activation for STE, assuming that the study can be efficiently completed. If regional wall motion abnormalities in a coronary distribution are present, then expedited CCL activation should be considered if the expected benefit from revascularization is estimated to outweigh the risk of deterioration from other non—cardiac-related illness. Importantly, if there is concern for progressive respiratory failure, we suggest that early intubation in a setting that minimizes risks of aerosolized material with subsequent exposure to hospital staff should occur and mechanical ventilation initiated in the ED or ICU as opposed to the CCL. If there is profound diffuse left ventricular or biventricular systolic dysfunction, it may be reasonable to consider CCTA to further delineate coronary anatomy vs continued supportive care.

In many health care systems, the role of CCTA in the immediate evaluation of STE in suspected or confirmed COVID-19 will be limited because of patient factors as well as constraints on time to study completion and interpretation. However, there are hospitals with a robust CCTA practice that are located in close proximity to the ED and can be expeditiously performed and interpreted by a cardiac radiologist or cardiologist. The role of CCTA is likely to be limited in the evaluation of STE, but in specific cases may add tremendous value in assessing coronary anatomy and determining the radiographic extent of lung involvement. However, the availability of CCTA needs to be considered in this context and may not be suitable for older patients who may have significant coronary calcification, for those who have severe tachycardia or tachypnea, and for those who are hemodynamically unstable.

On balance, a goal-directed echocardiogram may be clinically and logistically easier to obtain and result in less exposure to hospital staff. The value of a focused echocardiogram is highly dependent on the skills of both the sonographer and the interpreting echocardiographer, as an accurate evaluation of left ventricular regional wall motion abnormalities can be challenging even for an expert echocardiographer. Although point-of-care ultrasound is an excellent tool in the management of the acutely ill including those with COVID-19, we do not recommend its use in this setting, as the characterization of regional wall motion abnormalities is typically beyond the scope of most point-of-care ultrasound users. However, we strongly advise that the choice of echocardiography should be predicated on the availability of this service on a rapid basis and on the presence of an advanced sonography/physician team who can perform and interpret myocardial enhancement and/or perfusion echocardiographic imaging as a way to better evaluate wall motion and ventricular function.[19]

CONCLUSION

Myocardial injury in the setting of COVID-19 should be expected as there are observed cases of type 1 or 2 MI in the setting of acute infectious viral illnesses.[3,4,9,12,14] For patients with COVID-19, the evaluation can be challenging because of reports of STE without obstructive coronary disease, which creates diagnostic and management challenges.[5] Although the frequency of STE in COVID-19 remains unclear, it is important for institutions to define acute cardiac care pathways that balance the risks in patients with COVID-19 from invasive therapies and unnecessary contrast exposure vs the

Mayo Clin Proc. ■ June 2020;95(6):1107-1111 ■ https://doi.org/10.1016/j.mayocp.2020.04.005
www.mayoclinicproceedings.org

potential benefit if the patient is experiencing MI from acute coronary occlusion. The principle of "first do no harm" should apply to patient care and to the workplace in the CCL and hospital. The potential risk of a false-positive STE with CCL activation and exposure of CCL staff to a highly infectious agent must be taken in consideration as institutions and hospitals grapple with the need for patient-centered, ethical care. We believe that the strategy we propose will create slight delays in low probability patients, which reduce risks to patients and hospital staff, while allowing for invasive care if the diagnosis of a STEMI or type 1 MI is rapidly established.

ACKNOWLEDGMENTS

We thank Gayle Flo, APRN, CNP, for her contributions to our perspective.

Potential Competing Interests: Dr Jaffe has received consulting fees from Abbott, Beckman, Siemens, Roche, ET Healthcare, SphingoTec, Brava, Quidel, Blade, and Novartis (outside the submitted work). The other authors report no competing interests.

Correspondence: Address to J. Wells Askew, MD, Department of Cardiovascular Medicine, Mayo Clinic, Gonda 5-406, 200 First St SW, Rochester, MN 55905 (Askew.John@mayo.edu).

ORCID

Courtney E. Bennett: https://orcid.org/0000-0001-7186-1009; Mandeep Singh: https://orcid.org/0000-0002-9750-746X; Garvan C. Kane: https://orcid.org/0000-0002-4308-6356

REFERENCES

1. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published online ahead of print February 24, 2020]. *Lancet Respir Med*, https://doi.org/10.1016/S2213-2600(20)30079-5.
2. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state [published online ahead of print March 19, 2020]. *JAMA*, https://doi.org/10.1001/jama.2020.4326.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
4. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China [published online ahead of print March 25, 2020]. *JAMA Cardiol*, https://doi.org/10.1001/jamacardio.2020.0950.
5. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin [published online ahead of print March 16, 2020]. *Eur Heart J*, https://doi.org/10.1093/eurheartj/ehaa190.
6. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19) [published online ahead of print March 27, 2020]. *JAMA Cardiol*, https://doi.org/10.1001/jamacardio.2020.1096.
7. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78-e140.
8. Thygesen K, Alpert JS, Jaffe AS, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231-2264.
9. Cuervo G, Viasus D, Carratalà J. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378:2540.
10. Vasile VC, Chai HS, Khambatta S, Afessa B, Jaffe AS. Significance of elevated cardiac troponin T levels in critically ill patients with acute respiratory disease. *Am J Med*. 2010;123(11):1049-1058.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. 2020;395(10229):1038]. *Lancet*. 2020;395(10229):1054-1062.
12. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis [published online ahead of print March 10, 2020]. *Prog Cardiovasc Dis*, https://doi.org/10.1016/j.pcad.2020.03.001.
13. Sandoval Y, Jaffe AS. Type 2 myocardial infarction: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;73(14):1846-1860.
14. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart*. 2015;101(21):1738-1747.
15. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10(2):83-92.
16. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis*. 2009;9(10):601-610.
17. Szerlip M, Anwaruddin S, Aronow HD, et al. Considerations for cardiac catheterization laboratory procedures during the COVID-19 pandemic perspectives from the Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship (SCAI ELM) members and graduates [published online ahead of print March 25, 2020]. *Catheter Cardiovasc Interv*, https://doi.org/10.1002/ccd.28887.
18. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI Protocol. *Circulation*. 2007;116(7):729-736.
19. Porter TR, Mulvagh SL, Abdelmoneim SS, et al. Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography Guidelines Update. *J Am Soc Echocardiogr*. 2018;31(3):241-274.