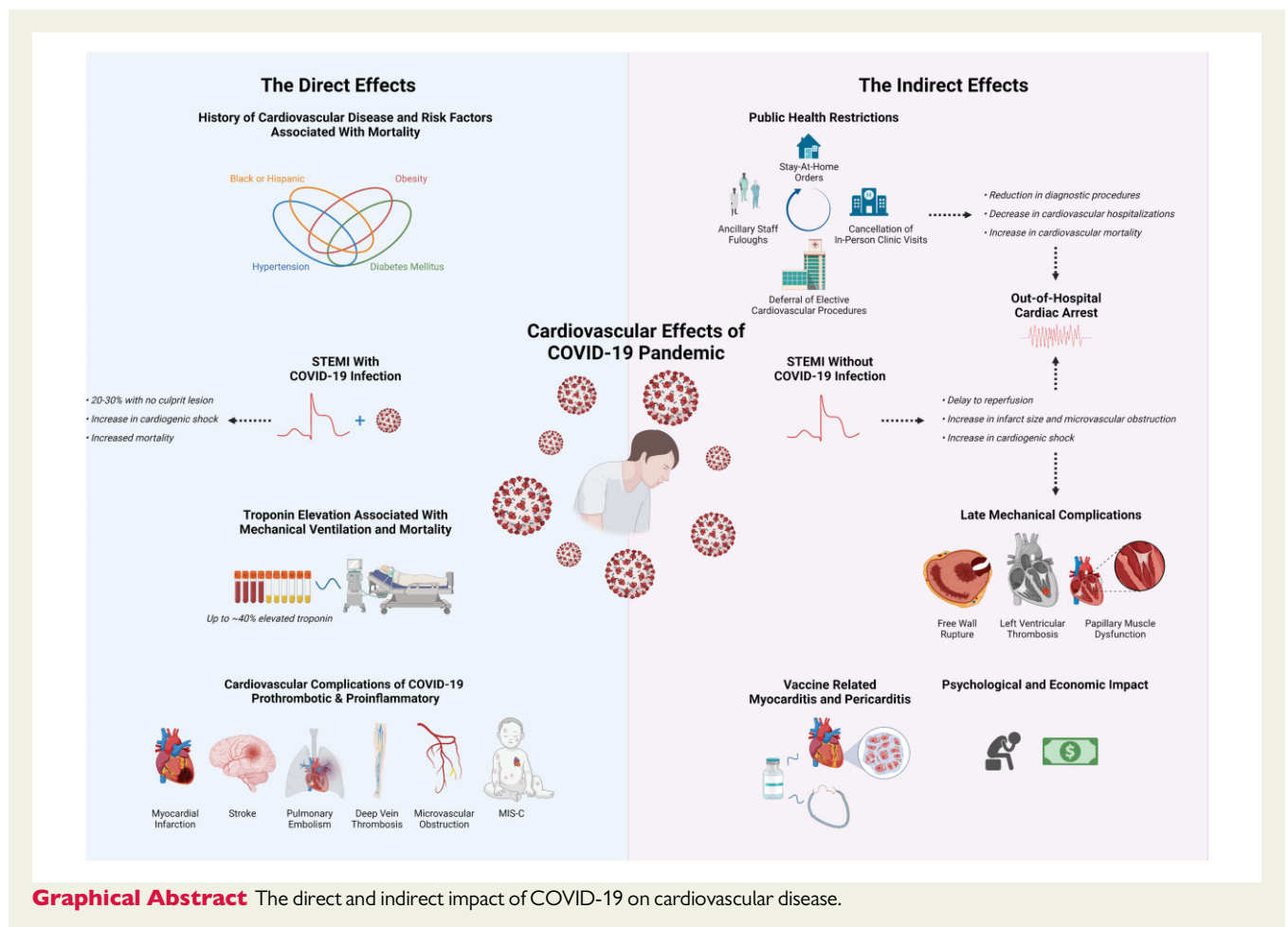


# The direct and indirect effects of the COVID-19 pandemic on cardiovascular disease throughout the world

Timothy D. Henry <sup>1,\*</sup> and Dean J. Kereiakes <sup>2</sup>

<sup>1</sup>The Carl and Edyth Lindner Center for Research and Education, The Christ Hospital, Cincinnati, OH, USA; and <sup>2</sup>The Christ Hospital Heart and Vascular Institute, The Christ Hospital, Cincinnati, OH, USA

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\* Corresponding author. The Carl and Edyth Lindner Center for Research and Education, The Christ Hospital, 2123 Auburn Avenue, Suite 424, Cincinnati, OH 45219, USA. Tel: +1 513 585 2017, Fax: +1 513 585 4857, Email: [Tim.Henry@thechristhospital.com](mailto:Tim.Henry@thechristhospital.com)

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The coronavirus disease 2019 (COVID-19) pandemic has perhaps had the most dramatic impact on worldwide healthcare in our lifetime.<sup>1</sup> This impact has been particularly complex for the cardiovascular community. The direct effects of COVID-19 infection are broad, often devastating, and include the following.<sup>2</sup> (i) Patients with pre-existing cardiovascular disease and risk factors, especially diabetes and hypertension, are at increased risk for mortality with COVID-19 infection. (ii) Between 20% and 40% of COVID-19-positive patients admitted to the hospital have elevated troponin, which is a major risk factor for in-hospital mortality, disease severity, and requirement for mechanical ventilation; the aetiology of troponin elevation is multifactorial.<sup>3</sup> (iii) COVID-19-positive patients have a spectrum of cardiovascular complications including thrombosis (deep vein thrombosis, pulmonary emboli, and large vessel stroke) and acute coronary syndromes including type 1 and type 2 myocardial infarction and occasionally myocarditis.<sup>2,4</sup> (iv) A unique direct effect of COVID-19-positive infection occurs in patients who present with ST-segment elevation, with a racial predilection for blacks, Hispanics, and indigenous populations, as well as patients with diabetes.<sup>5</sup> COVID-19-positive ST-segment elevation myocardial infarction (STEMI) patients are more likely to have no clear culprit artery on coronary angiography, have greater thrombus burden, are more likely to have in-hospital presentation, and have significantly higher mortality than do patients who are either 'under suspicion for COVID-19' or propensity-matched historical STEMI controls.<sup>5</sup> Of note, COVID-19-positive patients with STEMI were more likely to present in cardiogenic shock but did not have an increase in cardiac arrest compared with control patients.<sup>4,5</sup>

In addition, a myriad of 'indirect' or 'unintended' cardiovascular consequences related to the COVID-19 pandemic public health response have occurred.<sup>6</sup> These public health restrictions or 'lock downs' have included: (i) stay at home orders with recommendations to self-quarantine at home for 2 weeks if symptoms suggestive of COVID infection; (ii) cancellations of in-person clinic visits; (iii) deferrals of 'elective' cardiovascular procedures; (iv) staff layoffs due to the decline in cardiovascular hospitalizations and procedures; and (v) hospital policies that limited visiting, including immediate family.

Patient perception further influenced the provision of care, as patients often cancelled clinically indicated procedures due to fear of contracting COVID-19 in-hospital as well as the restrictive hospital visiting policies that would not allow family members to be present in the hospital. These indirect effects significantly impacted cardiovascular care. For example, by March 2020, it became apparent from social media reports that a significant reduction in patients presenting to emergency departments with STEMI had occurred.<sup>7</sup> Subsequent reports confirmed a 25–45% reduction in patients presenting with STEMI throughout the world that was associated with an increased incidence of out-of-hospital cardiac arrest.<sup>8</sup> It became apparent that patients with STEMI were avoiding the hospital and incurring the consequences at home. Similarly, there was a reduction in emergency department visits and a reduction in all cardiovascular admissions.<sup>9</sup> Further, a marked reduction in cardiovascular diagnostic testing occurred that was most pronounced in low- and middle-income communities.<sup>10</sup> Reports of mortality related to delay or deferral of structural heart disease procedures raised question as to whether or not treatment of symptomatic, severe aortic or mitral valve disease should ever be considered 'elective'.<sup>11</sup> Although a portion of the

increase in out-of-hospital cardiac arrests may have been directly related to COVID-19 cardiac involvement, the majority were likely to be related to patient avoidance of emergency departments and hospital care. Finally, those patients with STEMI who came to the hospital presented later, leading to higher rates of cardiogenic shock and mechanical complications.<sup>4,5,12</sup> Hospital treatment delays as well as altered protocols for treatment (use of fibrinolytics vs. primary angioplasty) have been implicated in the pathogenesis of these complications, but with limited direct proof.<sup>13</sup>

The report by Lechner and colleagues in the current issue of the *European Heart Journal* provides important insights into the pathophysiological impact of the COVID-19 pandemic on patients presenting with STEMI.<sup>14</sup> The prospective MARINA-STEMI cohort study (NCT0110411356) conducted at the heart centre in Innsbruck, Austria, enrolls patients presenting with a first STEMI who consent to undergo cardiac magnetic resonance imaging (CMR) as part of the trial. The authors examined CMR imaging from 474 STEMI patients enrolled between 2015 and 2020. Patients were categorized by time periods in 2020 with and without COVID-19 public health restrictions. Among the 48 STEMI patients admitted during three separate major COVID-19 health restriction periods in 2020, there was a significant increase in myocardial infarct size (22% vs. 14%,  $P < 0.01$ ), a higher frequency of microvascular obstruction (77% vs. 52%,  $P < 0.01$ ), a larger extent of microvascular obstruction (1.5% vs. 0.2%,  $P < 0.01$ ), and a higher rate of intramyocardial haemorrhage (56% vs. 34%,  $P = 0.02$ ) as compared with 101 patients who presented during time periods without major restrictions.<sup>14</sup> In addition, STEMI patients who presented during COVID-19 restrictions had significantly worse CMR findings than similar patients from pre-pandemic years 2015–2019. Patient characteristics were similar between groups with or without health restrictions except that patients who presented during times of restrictions had significantly longer total ischaemic times [263 min, interquartile range (IQR) 70–531 vs. 188 min, IQR 119–381 without restrictions;  $P < 0.01$ ] and a higher frequency of pre-intervention TIMI grade 0 flow (56% vs. 75%,  $P = 0.03$ ). These observations, gleaned from a prospective, ongoing CMR study in patients presenting with STEMI, suggest that delayed presentation with a subsequent increase in total ischaemic time, as occurred during periods of government-imposed COVID-19 restrictions, resulted in marked increases in myocardial infarction size (~8%), frequency, and extent of microvascular obstruction, as well as intramyocardial haemorrhage. Importantly, these CMR measures of myocardial infarct severity impact both short- and long-term prognosis following STEMI, and thus the longer term mortality ramifications of these findings are yet to be seen.<sup>6</sup> It is noteworthy that although total ischaemic time was significantly increased, the relative increase in door to reperfusion time between time periods analysed was not (median 12 min, IQR 7–41 without restrictions vs. 20 min, IQR 7–45 with restrictions;  $P = 0.51$ ). Although others have suggested that door to perfusion times have been prolonged during the COVID-19 pandemic, the present data support the premise that the major portion of time delay to treatment is patient related in the pre-hospital phase of care. Further study is required to determine the relative influence of patient delay in system activation due to fear of going to the hospital (fear of COVID-19) vs. delay in emergency medical system response due to lack of availability. The findings of delay to effective reperfusion and increased myocardial infarction size are consistent with the observed

increase in cardiogenic shock<sup>4,5</sup> and in mechanical complications of infarction (myocardial septal and free wall rupture, papillary muscle dysfunction and rupture, and left ventricular thrombus) that had become rare during the reperfusion era prior to the COVID-19 pandemic.<sup>12,13</sup> The inescapable conclusion is that, although the disease caused by COVID-19 is bad, governmental and health system responses to the virus may have a deleterious impact on cardiovascular care as well. Remediation of this pandemic response will require both public education and assurances of safety from COVID-19 infection during treatment for cardiovascular emergencies as well as potential moderation of hospital visiting policies to include at least one essential family member. Indeed, there is evidence that certain regions recovered faster than others using community education campaigns and focused standardized protocols for STEMI.<sup>15</sup> Through coordinated focus on both pre-hospital and hospital phases of emergency cardiac care, we can prevent the 'back to the future'<sup>13</sup> return of adverse outcomes considered rare in the modern era of timely reperfusion.

**Conflict of interest:** D.J.K. is a consultant for SINO Medical Sciences Technologies, Inc., CeleCor, HLT, Foldax, Elixir Medical, Svelte Medical Systems, Inc., Caliber Therapeutics/Orchestra Biomed, and Shockwave Medical, and is a stockholder in Ablative Solutions, Inc.

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