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.

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Editorial

Perioperative Cardiac Research Considerations During the Coronavirus Disease 2019 (COVID-19) Pandemic

THE CORONAVIRUS DISEASE 2019 (COVID-19) pandemic has dramatically changed the entire healthcare delivery system and conduction of medical research worldwide. At the beginning of the pandemic, many trials were forced to close abruptly, experiments were discarded, laboratories were temporarily shut down, and investigators became hesitant to start long-term studies due to the fear of potential lockdowns.[1,2] As of August, 2020, there remained a 20% decline from pre-COVID baseline in new patients entering cardiovascular trials, although this number is significantly improved from the 97% decline as reported in April 2020.[3] Recovery continues to vary greatly by geographic region and the research environment due to the varying impact of the disease and the local policies and responses that have adapted over time.[3] In concurrent fashion, the scientific community has diverted tremendous resources to projects involving therapeutic COVID-19 trials.

Challenges in perioperative cardiac research have arisen from quarantines, site closures, travel limitations, interruptions to the supply chain of the investigational product, and COVID-19 infection in site personnel and trial participants. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.[4,5] The National Institute of Health, United States Food and Drug Administration, and other funding agencies have provided guidelines for clinical trials affected by COVID-19.[4,5]

Planning the Research

Clinical Trial Design

Although the rapid development and recruitment for COVID-19 trials undoubtedly has resulted in success and is a testament to the worldwide research community, the rushed nature of this research has led to much duplication and production of many poor-quality trials. Most initial COVID-19 clinical trials were open label, few were placebo-controlled, results were often preliminary, and, at many times, published data did not benefit from peer review. Therefore, a significant number of reports have limited use to clinicians or patients as they frequently have led to incorrect conclusions, which subsequently were invalidated by well-designed large, randomized controlled trials.[6] Notably, in the rush to disseminate knowledge, prestigious journals, such as the New United Kingdom Journal of Medicine and The Lancet, have retracted previously published articles, which were seen as major COVID-findings at the time of publication.[7,8] A full list of retracted COVID-19 papers can be found at Retraction Watch.[9] Double-blinded, randomized controlled trials, whether new or repurposed, preferably with a placebo comparator should be designed, even though the pandemic adds challenges to these constructions. Large, long-term trials that establish standards for drug treatments are of such vital importance to the public health that every effort, including investigator blinding, should be built into the trial design to produce valid results in studies of the highest reliability and the clearest interpretation.

Research Cost

As a result of COVID-19, researchers may incur unanticipated costs, such as costs to arrange for participants to receive care virtually or at alternative sites, supply chain disruptions, personnel disruptions due to illness or closure of facilities, additional laboratory testing (eg, for COVID-19), and increased transportation costs. Renegotiation might be needed with the sponsor to cover this necessary spending.

Patient Behavior

Patient behavior has changed markedly due to fears of infection and social distancing mandates by local authorities, leading to decreased medical care and altered nonfatal event rates. For example, the COVID-19 pandemic temporally was associated with a 40% decrease in presentation for acute coronary syndromes.[10,11] Heart failure hospitalization rates have dropped up to 50% with regional COVID-19 spread and governmental activity restrictions.[12] Selection bias is a significant concern in clinical investigations of patients presenting to surgery, as this cohort may not be representative of the general

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population. In addition to the reduced potential pool for perioperative research, some studies lack feasibility due to patient fears related to travel and social interaction, as well as hospital restrictions.

Care Personnel

During the pandemic**,** disease-specific care teams were altered to accommodate the intensity of COVID-19 admissions and care. For example, nationally and internationally, many internists, hospitalists, anesthesiologists, surgeons, and cardiologists joined the COVID-19 care teams to support their colleagues to prevent the overburdens. These efforts likely impacted the regular expert teams' usual access to cardiovascular illnesses and associated events. Additionally, the efforts to decrease trainee burdens may have further challenged the manpower of academic centers' proper care for cardiovascular problems.

Implementing the Research

Safety

The safety of trial participants and research staff is of paramount importance during COVID-19. Investigators, sponsors, and local institutions need to decide on the safety of continued trial subject recruitment, use of investigational products (nature of disease, supply chain issues, withdrawal risks from investigational treatment), and novel strategies for follow-up visits and patient monitoring methods (phone contact, virtual visit, alternative location for assessment). Research staff and/or investigators also must follow strict local isolation and social distancing policies to reduce the spread of coronavirus. The National Institutes of Health recommend the following: (1) limiting study visits to those needed for participant safety or coincident with clinical care, (2) conducting virtual study visits, (3) arranging flexibilities for required laboratory tests or imaging needed for safety monitoring to occur at local laboratories or clinics, (4) canceling large gatherings of 50 or more people, and (5) limiting or suspending unnecessary travel.

In addition to limiting the number of visits, there are recommendations about the quality of visits due to the concerns on physical distancing (safe distancing), limitations on cumulative total contact time, and aerosolization in poorly ventilated indoor areas, which form a further safety threat to research practices.

Protocol Change

Sponsors and investigators should engage their institutional review board prospectively or as soon as possible when changes to the protocol are needed due to COVID-19. Alternative processes should be documented and contingency plans described. It is important to detail the expected duration of proposed changes and how these changes are related to COVID-19. Denoting which trial participants are impacted and how their participation will be specifically affected also are necessary. In addition, alternative delivery methods, such as study trained-home nursing and alternative privacy compliant sites, can serve as temporary solutions, with a similar amount of research accountability. Furthermore, changes in study visit schedules, missing patient data, and disease-related discontinuations may lead the investigators to revisit their study protocols.

Informed Consent

The COVID-19 pandemic has altered the traditional in-person, physician-to-patient interaction, as hospital masking and visitation policies have created both physical and interpretation barriers to communication. This has necessitated enhanced reliance on telephone or videoconferencing as means to identify, recruit, enroll, and consent for research protocols. While current masking procedures may hinder face-to-face communication and interpretation of information, telemedicine has the advantage of allowing unencumbered facial recognition and mutual awareness of effect. As telemedicine becomes more entrenched in clinical research programs, ongoing consideration must be made for the following concepts: (1) patient understanding and appreciation of disclosed information, (2) perception of the consent process, (3) ample time for decision-making, (4) patient perceptions of coercion and voluntary decision-making, and (5) research recruitment rates. Further study is required to fully appreciate the effect of telemedicine in these areas.[13]

Data Collection

Sponsors and contract research organizations increasingly have implemented remote monitoring during the pandemic to collect data and ensure integrity, with adherence to Good Clinical Practice guidelines. However, collecting study data remotely has been challenging for investigators. Digital remote recording of certain exertional and functional measures are possible, such as accelerometer-based activity for timed walking tests.[14] However, measurement error, poor device reliability, lack of performance testing, missing data, and the needed patient reminders to wear nonimplantable devices to record activity are limitations that can cause data inaccuracy. Wearable technology also could have psychological consequences that alter behavior, and it is unclear whether data from different modalities can be pooled. Mask-wearing may also affect performance and must be a consideration. In addition, activity data from implantable devices may cause data imbalance between groups, as many participants lack these devices.[15] Additionally, interchangeability of these devices or the quality and the compatibility of data driven from different devices, are not known at this point. To facilitate analysis, it is best to record the mode of test administration, modifying only as necessary to maximize data collection while maintaining procedural integrity. For example, the New York Heart Association functional class may be assessed remotely, but the means of collection should be recorded, and its value to clinical trials

should continue to be reexamined and compared to data collected in person.

Analyzing the Research

Outcome Considerations

Many COVID-19-related factors might confound perioperative cardiac research endpoints and complicate event adjudication and data interpretation. COVID-19 diagnosis, symptoms, duration, resolution, hospitalization, and complications must be recorded accurately and discerned from cardiovascular complications.[16] Information on COVID-19 status at the time of study aids in data assessment, including: (1) whether the patient was definitely positive for COVID-19, (2) definitely negative, (3) unknown but suspected positive, or (4) unknown and suspected negative. Prospective and retrospective collection of COVID-19 infection status, which may include nucleic acid and serologic testing, as well as documentation of symptomatology and related health events, should be performed to aid analysis and interpretation of the data. Investigators should determine whether COVID-19 was noncausal, contributory, or the primary cause of cardiovascular and noncardiovascular events.[17]

Mortality Rate

Fear of hospitalization and inaccuracy in death recording at home may artificially reduce mortality rates in conducted research, which is one of the most important research endpoints. Patients living in long-term care facilities may have a higher chance of exposure to COVID-19, with increased mortality from COVID-19 death not counted toward cardiovascular-related death. In countries with COVID-19-related financial assistance programs, more deaths likely are attributed to COVID-19 instead of primary cardiovascular causes secondary to monetary considerations. Patients delaying presentation to the hospital and missing health maintenance appointments due to COVID-19 restrictions and infection concerns likely are increasing the true incidence of cardiovascular-related death. Potential reasons of how cardiovascular mortality outcomes are impacted during the pandemic: (1) due to COVID-19 scare, decreased hospital admissions and increased mortality at home or nursing home with unexplained cause; (2) masked cardiovascular event behind in-hospital COVID-19 deaths; (3) increased COVID-19 admission diagnoses due to federal financial coverage; (4) unrecognized cardiovascular COVID-19 death in insufficiently monitored beds; and (5) lower listing of cardiovascular death in the priority ordering of cause of death.

Admission and Readmission Rate

COVID-19 likely is affecting historic comparisons of cardiovascular admission and readmission rates as fear of contracting COVID-19 has kept some patients at home. In addition, hospitalizations might be attributed to COVID-19 in lieu of cardiovascular reasons when coexisting diagnoses exist. Decreased physical activity due to home lockdowns and quarantine may have, in fact, reduced the quantity of cardiovascular events, or impacted the severity of cardiovascular symptoms and related admission rates.

Cardiovascular Events

COVID-19 infection itself may worsen cardiovascular-like symptoms such as dyspnea, chest pain, and dizziness. For exertion-related events, lifestyle changes with home lockdown and/or social distancing may substantially reduce overall physical activity and exertional tolerance. To complicate the matter further, COVID-19 infection and associated inflammation might increase risk of thrombosis, heart failure, myocardial infarction, and myocarditis.[16,18] There remains concern that certain cardiovascular medications may augment COVID-19 infection by aiding the virus in entering the cells via the angiotensin system.[19] However, recent randomized control trial demonstrated that between patients hospitalized with mild-to-moderate COVID-19 and who were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before hospital admission, there were no significant differences in the mean number of days alive and out of the hospital for those assigned to discontinue versus continuance of these medications.[20] Furthermore, due to the loss of employment from economic lockdown and social restrictions, some patients may be unable to obtain appropriate therapeutics, thus leading to new and/or recurrent cardiovascular events and death.

Renal/Pulmonary Events

Due to the multisystem impact from COVID-19, renal injury and pulmonary injury are common from COVID-19 and might not be possible to discern from trial-related interventions.

Biomarkers

COVID-19 complicates biomarker usage in cardiovascular research because infection is associated with increased circulating levels of common indices, and biomarkers denote risk for severe COVID-19 disease and worse outcomes.[16,18] Although, in many patients, biomarker changes appear to be due to noncardiac critical illness, this coronavirus appears to have tropism for the myocardium and vasculature.[12] Thus, COVID-19 complicates adjudication of myocardial injury events and worsening cardiovascular events because the symptomatology and biomarkers may be consistent with either COVID-19 or primary cardiovascular conditions.[17]

Statistical Analysis

For a trial that has enrolled few patients, sponsors may consider either substantially revising the statistical plan, or designing a new trial to begin after the COVID-19 pandemic has waned sufficiently in order to account for changes and/or

challenges in the current clinical trial environment. Statistically accounting for the timeline and intensity with which COVID-19 affected local or regional clinical care and patient behavior, could help adjust for the comprehensive changes in healthcare utilization and efficacy associated with the COVID-19 pandemic, including increased overall mortality rates, decreased healthcare utilization, and excess cardiovascular mortality due to COVID-19. Overall, incidences of common medical illnesses, their hospital admission priorities, routine clinic follow-up visit practices, and chronic disease admissions likely are changed to a great extent during the lengthy pandemic period. In short, the whole annual statistics for chronic illnesses may have been significantly impacted during the pandemic. Therefore, chronic illness projections and comparisons to previous years may provide unrealistic and unfair results. It is likely that for chronic disease statistics, the COVID-19 period should be assessed only within and not with other periods.

Research Opportunities for Anesthesiologists

Although this pandemic has brought about enormous challenges for cardiovascular research, COVID-19 also has created many potential unique investigational opportunities for cardiac anesthesiologists. A few of the discovery potential subjects are:

1. Long-term cardiovascular effects of COVID-19; serial echocardiographic assessments in recovery-based intervals.
2. Long-term pulmonary effects of COVID-19.
3. Optimal anesthetic management of COVID-19 patients in thoracic and cardiac surgery.
4. Mechanical ventilatory support options for severe COVID-19 patients.
5. Clinical outcomes, risk factors and improvement strategies for active or recovered COVID-19 patients undergoing surgery.

In conclusion, the unprecedented COVID-19 pandemic has dramatically impacted the scientific community and imposed significant impediments to scholarly inquiry. High-quality, innovative, and adoptable discovery research in both cardiovascular and COVID-19 projects remain desperately needed. Anesthesiologists have a great opportunity to be at the front line of these efforts in providing safe patient care and solution-generating clinical research.

Conflict of Interest

All authors declared no conflict of interest.

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