COVID-19 and the Heart: Knowledge 'Evolving by the Hour'

Round Table
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The world is in the midst of the COVID-19 pandemic caused by a novel coronavirus, SARS-CoV-2. The popular media mainly considers the virus's respiratory manifestations, but evidence has emerged that it also has major effects on the CV system. Patients with preexisting CV conditions have elevated risk when they contract COVID-19, and the viral infection can cause cardiac dysfunction, sometimes leading to CV death in the worst cases.

Therefore, understanding COVID-19 and SARS-CoV-2 is imperative for the cardiology community, and beyond. To that end, Cardiology Today and Healio convened a panel of experts from a variety of backgrounds, including basic science, virology, vascular biology, pathology, HF {Heart Failure}, arrhythmia disorders, cardio-oncology and cardiac intensive care, to discuss the CV implications of COVIDl9 and the virus that causes it.

The expert panel addressed topics such as the role of the angiotensin-converting enzyme 2 (ACE2) pathway in the disease and its relevance to the CV system, the stages in which the disease progresses and the CV implications of each stage, the role of endothelial cells in progression of the disease, the use of CV biomarkers to assess risk in patients with suspected COVID-19, the manifestations of myocarditis seen in patients with the disease, possible causes of cardiac dysfunction, the relationship between COVID-19 and acute MI {Myocardial Infarction} and the cardiac adverse events associated with potential treatments for the disease.

The virtual roundtable was held on April 20 and 21, with breaking updates added before the press date. The discussion has been edited for clarity and space.

Editors note: Developments in the COVID~19 pandemic are quickly evolving. Information in this article was up to date at the time of publication. To access the latest updates, visit Healio's COVID-19 Resource Center at www.healio.com/coronavirus.

Understanding the ACE2 system

Carl 1. Pepine, MD, MACC: Since December, the world has been inundated by this novel virus, which most think is only a respiratory virus. However, those of us in cardiology have realized that there are many CV implications. Dr. Raizada, you have spent your career studying the renin-angiotensin system and were one of the first to work with the ACE2 system, which is believed to be the major entry point of this virus into the pulmonary system. Can you put the ACE2 system into perspective?

Mohan K. Raizada, PhD: It is important to review the vasoconstrictor, proliferative and inflammatory arm and the vasoprotective arm of the renin-angiotensin system. We are all familiar with the key enzyme ACE and the conversion of angiotensin I to angiotensin II, ACE inhibitors inhibiting that enzyme, and then angiotensin II interaction with the AT1 receptor. The activation of the AT1 receptor results, causing inflammatory, hypertrophic and hypertensive actions.

ACE2 is expressed in most of the CV-relevant tissues and organs. The highest concentration of ACE2 is in the epithelial cells of the lungs and the gut. More recent observations have shown that pericytes in the heart, cells that envelop micro-vessels, also express very high concentration of ACE2, with implications on effects on the heart.

The loss of ACE2 exacerbates CV and other complications. For example, in the heart and the kidney, it increases reactive oxygen species, hypertrophy and inflammation.

ACE2 is a trans-membrane enzyme that has a receptor binding domain and a protease domain. The most important thing to remember is that SARS-CoV-2 binds to the receptor binding domain, which is different from the ACE2 activity domain.

There are three components which are important in the virus's entry into the cell: the virus, the ACE2 and the secretase ADAM17 {a disintegrin and metalloproteinase-17} plus the enzyme trans-membrane protease serine 2. TMPRSS2 {Transmembrane protease, serine 2} clips off some of the part of the virus, which leads to its interaction with ACE2. And that interaction leads to its internalization.

As a result, the membrane ACE2 and ACE2 levels are decreased. There is another aspect whereby the secretase ADAM17 can clip off the enzyme and release the soluble form of ACE2. There are some indications that the soluble ACE2 may act as a sink or a decoy to bind circulating viruses and eliminate them. The bottom line is that the major component or regulation of viral entry into the cell in addition to ACE2 are the ADAM17 and TMPRSS2. Entry into the cell obviously leads to all the bad effects of this virus.

Pepine: A clinical concern is, should angiotensin receptor blockers and ACE inhibitors be continued in patients who get COVID-19?

Raizada: My feeling is, lacking any data, the decision to continue angiotensin receptor blockers and ACE inhibitors at the moment is a good one, because all the basic science tells us is that these drugs should have a beneficial effect, because they will decrease the Ang-II pathway and increase the ACE2 pathway. So, unless we find that there are adverse effects from the clinic, I would think that these medications need to be continued until we have the evidence otherwise.

Mandeep R. Mehra, MD: Three studies published in *The New England Journal of Medicine* in early May have found no association of the risk for infection, severity of infection or in-hospital outcomes with use of these drugs in COVID19. My group published an analysis of in-hospital mortality risk in 8,910 patients hospitalized with COVID-19 across three continents. The other two groups assessed risk for infection and severe infection. One performed a case-control study with 6,272 infected participants and the other studied 5,894 people that tested positive for COVID-19.

Pepine: The ACE2 is sex-linked; the gene resides on the X chromosome. Interestingly, most of large series reports (China, Italy, New York, Iceland, etc) of those hospitalized with COVID19 show a predominance of men. So, what is protecting women from this virus?

Raizada: The thinking has been that either men are able to eliminate soluble ACE2 from their circulation, thus rendering it less protective, or the enzyme is under the control of sex hormones. There are some data which show that androgens regulate this enzyme. It may be possible that there is an androgen-mediated decrease in ACE2 in men, but it is all hypothesis at this stage.

Stages of illness

Pepine: Dr. Bohula, you are on the front lines with COVID-19 as a CV critical care specialist, please comment on what you are currently seeing.

Erin A. Bohula, MD, DPhil: As Dr. Raizada outlined, there are manifestations of this disease in multiple organs. We're seeing predominantly pulmonary manifestations and severe, profound and refractory acute respiratory distress syndrome (ARDS), where patients are on ventilators for 2 to 3 weeks.

We've also seen some precipitous, acute CV manifestations, including thrombotic coronary epicardial disease or ACS, and also a clinical picture that looks like myocarditis with profound ECG changes, troponin elevations and myocardial dysfunction without epicardial disease.

With a mind to potential therapeutics, we think it will be helpful to consider the viral life cycle as well as the body's response to the virus. A theory has been proposed that there are multiple stages to this specific illness, including a viral and an inflammatory phase (figure, page 10). In the early stage, viral replication manifests as the classic constitutional symptoms of a viral illness. That would be when to focus on using antiviral agents. In the context of this progressive viral illness, ultimately there is an inflammatory response, both humoral and cellular, which should lead to resolution of the illness. But sometimes, patients can have a pathologically robust inflammatory response and it may be the hyper-inflammatory phase which drives much of the multi-organ system failure that we're seeing, including ARDS and CV complications. We hypothesize that the hyper-inflammatory response may be treated with targeted anti-inflammatory therapies.

There are several steps in the Viral life cycle that may represent a mechanistic target for antiviral therapeutics, including viral particle binding to the host cell through the ACE2 receptor, endocytosis, endosomal maturation and cytoplasmic release of viral RNA, proteolytic cleavage of viral proteins, replication of the viral genome, viral capsid assembly and exocytosis. Studies are ongoing with several agents hypothesized to block one or more steps along

the life cycle, such as neutralizing antibodies, JAK2 {Janus Kinase 2} inhibitors, hydroxycholoroquine, protease inhibitors and remdesivir (Gilead Sciences) and other nucleotide analogues (Table 1, page 12 and Table 2, page 13).

So, COVID-19 seems to be a multi-phase disease, at least in the patients that I'm seeing in the ICU, who obviously have the most severe manifestations of this illness.

Cardiac dysfunction

Pepine: Dr. Mehra, as an authority on HF, please discuss the cardiac dysfunction that can result.

Mehra: There are a number of interesting observations. The first is that people who have underlying CVD {cardiovascular disease}, be it HF, underlying CAD {coronary artery disease} or even history of a cardiac arrhythmia like atrial fibrillation, seem to have a much more vulnerable course once they're infected with SARS-CoV-2. The second is that in 20% to 30% of patients hospitalized with COVlD-19, by around day 4, we see a rise in markers of CV injury. This biomarker, troponin, is a strong negative prognostic marker suggesting that there is interplay between CV complications with COVlD-l9 and death. Therefore, COVlD-l9 is not just a pulmonary disease.

There may be an interplay from a variety of different constructs. One syndrome presents like an ACS. In such cases, a coagulation disorder with an occluded coronary artery is noted. Far more commonly, we note a myocardial component, wherein patients present with ST-segment elevation and often have "normal-appearing" coronaries. We do not have a lot of data with myocardial biopsies because those often deferred during the acute illness. In the few autopsy series available, there is little evidence of the virus in myocardium or in a pattern of lymphocytic myocarditis. So, it begs the question of why and how these patients develop an acute cardiomyopathy. It may very well be that this is an immune-related complication or perhaps a stress-related cardiomyopathy.

There are a number of pathways by which cardiac dysfunction can occur in this syndrome. It can occur through direct coronary injury; through a takotsubo-type presentation {due to stress and high circulating levels of epinephrine} that one sees in critical illness; through a cytokine storm or the immune process that can lead to myocyte and cardiomyocyte depression; or it could be from direct viral engagement of the myocardium or its tissues. We are only now learning about these issues. This then begs the question: Is there something we can do if this is in fact a vascular disease or in many ways a CV disease and a myopathic disease? Can we give medications that perhaps are useful in these conditions?

'Havoc' in the CV system

Pepine: Dr. Libby, as an expert in pathophysiology and vascular biology, can you address the systemic and local responses to cytokine storm and other phenomena?

Peter Libby, MD: I view the inflammatory and immune response as a "frenemy." We count on these mechanisms to defend us from invaders, stanch hemorrhage and repair injury. Yet, when these usually protective functions spin out of control, if our own immunological foot soldiers, the inflammatory cells, and the messengers that they elaborate become hyperactive, we can have a positive feedback loop where inflammation begets inflammation. The inflammatory response then is no longer adaptive, but it can actually lead to some of the complications that give such devastating outcomes in this very virulent virus.

The surface of the endothelial cell has numerous properties that can keep blood in a liquid state during prolonged contact. The mechanisms include anticoagulant and profibrinolytic functions. But when the endothelial cell encounters some of the cytokines produced in situations like COVID-19 infection, it changes its character from one that can defeat thrombi by fibrinolysis and inhibit the formation of thrombi, to exhibit prothrombotic and antifibrinolytic functions. Overwhelming infections boost the production of cytokines such as tumor necrosis factor (TNF) and interleukin-l (IL-1) that flip that balance from anticoagulant to a fibrinolytic anti-thrombotic to the opposite, favoring thrombus accumulation. This may be important in some of the pulmonary complications; microvascular complications in the lung, kidney and heart; and macrovascular complications, including a thrombotic diathesis in the larger veins.

These cytokines can accelerate atherogenesis by activating inflammatory cells that inhabit plaques and precipitate destabilization and a type 1 MI.

But there is also danger of having type 2 MI situations with decreased oxygen supply and increased oxygen demand. Infections cause tachycardia and fever, which increase oxygen needs, but at the same time sepsis, including the final stage of COVID-19, with or without a bacterial super-infection, can cause hypotension and profound hypoxemia due to the rampant pneumonitis. This imbalance between oxygen supply and demand can lead to a type 2 ACS.

Acute infections can thus wreak havoc on the CV system, precipitating type 1 or type 2 ACS; direct infection of the myocardium as discussed by Dr. Mehra; vascular dysfunction, including vasoplegia; decreased endothelial vasodilatory function; and micro and macrovascular thrombosis. The cytokine storm in late COVID-19 disease, an out-of-control inflammatory response, has devastating consequences, not only for the lungs, but also the CV system and other organs including the kidneys.

Mehra: Perhaps COVID-19 is not just a pulmonary disease or an immune disease, but is actually an endothelial cell disease and a vascular disease. Would you agree with that?

Libby: Sure. We've known for decades that ACE2 is highly expressed on pulmonary endothelial cells. That ACE2 could be expressed by CV cells is more recent, as Dr. Raizada mentioned. But I think that that's very likely and it fits right into the idea of disturbing the interface of the endothelial cell with the blood.

The role of myocarditis

Pepine: Dr. Moslehi, can you speak about the very critical CV outcome of fulminant myocarditis, which you have experience with in the cardio-oncology area, and if you have seen anything resembling this in COVID-19?

Javid Moslehi, MD: Drugs that modulate the immune system have emerged as important cancer treatments. This has affected the cardio-oncology space, where many of the observed CV sequelae did not exist previously. For example, a few years ago, our group defined the syndrome of fulminant myocarditis after treatment with immune checkpoint inhibitors (ICI). In the classic definition of the word, this is truly myocarditis: myocardial infiltration, mostly with T cells and macrophages and myocyte death. The patients can become very sick very quickly and have arrhythmias. With ICI, we see other inflammatory syndromes such as vasculitis and pericarditis.

In contrast, another class of immuno-therapies, cell-based therapies for example, chimeric antigen receptor (CAR) T cells therapies or bispecific antibodies can cause cytokine release syndrome, which can affect multiple organs, including endothelial cell and myocardial damage. Work that one of my recent cardio-oncology fellows, **Joe-Elie Salem, MD, PhD**, now in France, has completed and which will be published soon, demonstrates using large databases a myriad of CVD manifestations with CAR-T cell therapy. In my laboratory, we are building cell-based and mouse models of these new inflammatory cardio-oncology platforms, which hopefully will teach us a bit more about the overall intersection of the immune and CV systems.

This is all very relevant to COVID-19, of course. I would say that at this point, the jury is still out on whether the myocardial damage with SARS-CoV-2 is classic myocarditis where SARS-CoV-2 infects either a cardiomyocyte or other cell types such as pericytes and fibroblasts in the heart, leading to an innate immune response, which leads to classic myocarditis—or excess cytokine release leading to either direct cytokine damage or antibody-mediated damage. We need additional clinical data at this point to determine which type of myocardial damage we are actually seeing. If I had to put my money down, I would say that cases of myocardial injury and myocarditis more resemble what we see with CAR-T cells.

Biomarkers

Pepine: Dr. Jaffe, you have spent your career studying biomarkers. Please discuss cardiac troponin elevations and N-terminal pro-B-type natriuretic peptide in the setting of the cardiac injury that is being seen very frequently in patients with COVID-19.

Allan S. Jaffe, MD: Those of us who worked in biomarkers and studied critical illness for years know that patients who are critically ill often have elevated troponins. This is well known in the acute respiratory failure realm. Once one has acute

respiratory failure with hypotension and acidosis and hypoxia, the frequency of elevations is nearly 50% in published literature, not having anything to do with coronavirus. Much of this is direct myocardial injury having to do with a variety of mediators such as TNF, heat shock proteins and cytokines. These increases are best termed “myocardial injury.” Some increases also likely are due to supply, demand and balance and type 2 MI, when ischemia is present.

If one just takes those data from the prior literature, and adds the concept that the virus causing COVID-19 seems to infect those with CVD differentially, one should have expected a huge incidence of elevated troponins in almost all of these patients due to the acute respiratory failure and since with high-sensitivity assays, patients with more severe underlying CVD often have increases in troponin related to the extent of the underlying structure of cardiac disease. These increases have negative prognostic influences absent COVID-19 and are likely synergistic with additional stress of respiratory failure.

What makes COVID-19 so much more interesting is that there are additional findings to hypothesize a variety of other possibilities. There are likely cases of takotsubo cardiomyopathy with modest elevations in troponin and gargantuan increases in natriuretic peptides.

It is also theoretically possible if one looks at cross-talk between some of the inflammatory responses, there ought to be more type 1 M1.[5] However, thus far, data suggest that we are not seeing more type 1 M1[3]; we fear that some of those patients are staying at home and we’re missing them. But in fact, we’re seeing many more circumstances of ST-segment elevation in the absence of CAD or type 1 events. What are those?

One possibility is myocarditis. It’s well described to present this way with very high mimetic-like troponin levels. Despite that, the number of pathologic cases or even MRI-determined cases showing myocarditis is relatively modest. There are other possibilities as well. Many of these patients have very high levels of D-dimer. The thought is that they have micro-thrombi, which are well documented in the lung but less well documented in the heart. So, one can make a strong case for use of anticoagulants if pulmonary thromboembolic disease is suspected. It’s much more difficult to make this case for the heart, thus far. but it is an attractive hypothesis that microvascular thrombi could cause ventricular dysfunction. We worry about these possibilities clinically, but it’s not clear whether that’s microvascular disease or concomitant sepsis, the higher the troponin, the worse the prognosis, and the greater the change in troponin, the worse the prognosis.

What to do specifically is less clear. It depends on the mechanism. Using troponin, and BNP if it’s rising, might be one good way to determine if we need to do further evaluations because we see CV abnormalities that may require investigation. Interestingly, NT-proBNP and cytokine measurements are not as prognostic in this particular circumstance as is troponin, but they probably give you a signal in regard to mechanism.

Timothy D. Henry, MD: I think we should encourage people to measure troponin for early risk stratification.

Jaffe: I agree with that wholeheartedly, but there’s a caveat. The idea of using a high or rising troponin value to identify a high-risk patient is really good, but I am not sure we should rely on a low value equally well for defining a low-risk patient, given that COVID-19 can be progressive in nature.

Acute MI and COVID-19

Pepine: Dr. Henry, you have spent years treating emergency cases in the cath lab. Can you talk about CAD, coronary artery dissections and stress-related cardiomyopathy?

Henry: A few months ago, we would have expected to see an increase in MI. We know with influenza, there is an increase in MI related to coronary plaque rupture. With COVID-19, there are both prothrombotic effects and STEMI mimic like myocarditis.

In stress-related events such as hurricanes or earthquakes, there is always an increase in MI, from plaque rupture, stress cardiomyopathy and spontaneous coronary artery dissection. So, we would have expected to see an increase in STEMI activations during the COVID-19 pandemic. Instead, very early from social media and across the world, we saw a marked decrease in STEMI activations. We recently published our results in the *Journal of the American College of Cardiology* from nine large STEMI

systems across the United States. Remarkably, both in high-prevalence and low prevalence COVID-19 areas, there was a significant reduction in activations in all nine STEMI systems; nearly a 40% reduction in STEMIs. That observation has now been reproduced in Spain, Austria and northern Italy.

So where are the missing STEMIS? It's well documented that we have an increase in late complications of STEMI. I've probably seen more ventricular septal defects and papillary muscle ruptures in the last month than I have in the last 15 years. There is also an increase in left ventricular thrombus and an increase in HF admissions at our institution, because patients are scared to death about going to the hospital. This is an important public health problem.

Another hot topic is the optimal treatment for these MIs. There has been a lot of discussion about using lytics. But a consensus statement from the Society for Cardiovascular Angiography and Interventions, the ACC and the American College of Emergency Physicians emphasizes strongly the belief that patients with COVID-19 should have standard treatment. Lytics should be reserved for patients who are going to have a known delay to go to the cath lab. The ideal treatment should be still primary PCI, with some thoughtfulness about which patients you take.

The availability of rapid testing for COVID-19 is increasing and is greatly helping to determine treatment for these patients.

A problem is the paucity of data available. Therefore, we've started the North American COVID Myocardial Infarction (NACMI) Registry, a partnership between the Canadian Society of Interventionalists, SCAI and the ACC Interventional Council. About 150 sites across Canada and the United States are sending deidentified data on their patients with ST-segment elevation and left bundle branch block. We will soon be able to have some better insights into this issue.

A recent report in NEJM {New England Journal of Medicine} discussed 18 patients with COVID-19 and ST-segment elevation. Of note, these patients never went to the cath lab and there was extremely high mortality, more than 70%. Many of the ST-segment elevations developed during hospitalization, as Dr. Jaffe mentioned. COVID-19 clearly has changed the landscape for acute MI.

Bohula: What about the logistics of timing for the cath lab? At Brigham and Women's Hospital, there is difficulty with door-to-balloon times in COVID19-positive patients.

Henry: There is a report from Hong Kong with only seven patients showing that time from symptom onset to presentation was excessively delayed. We're seeing even longer delays in the U.S., with people coming days later because they're afraid to come to the hospital.

Once they get to the hospital, the door-to-PCI times are also delayed. This can happen in high-prevalence areas where the ED {Emergency Department} is overwhelmed. Or it can happen across the country because people are concerned about whether this is a patient with COVID-19 because of overlap in symptoms.

What we've tried to get across in the guidance document is that while we have relaxed the standard door-to-balloon time of 90 minutes, we still encourage less than 120 minutes.

I would encourage testing—rapid testing if you have it available. Point-of-care ultrasound can be very helpful. Then, going to cath lab as quick as possible. Importantly, with appropriate personal protective equipment (PPE). Another thing that we have been working on with SCAI is, what is the exposure to risk? And it appears now that if you have appropriate PPE, patients can be treated safely in the cath lab.

Impact of stress, disparities

Pepine: Dr. Bairey Merz, can you talk about stress-related cardiomyopathy and speak to some of the disparities we are seeing in patients with COVID-19?

C. Noel Bairey Merz, MD: It would not shock me to see more cases of takotsubo cardiomyopathy triggered by this infection. It is interesting that STEMIs are down. Takotsubo cardiomyopathy can be confused with a STEMI. Especially if a patient goes into shock, it looks like a major MI. It is not until the patient gets to the cath lab that we know for sure. The possibilities are the obvious that people with STEMI or takotsubo cardiomyopathy just don't come to the hospital because they're so afraid of contracting COVID-19. But there is an alternative explanation: There is

something unique about this prodrome before the cytokine storm that somehow is not causing STEMIs.

As for why this disease appears to be harming women less than men, our prior experiences such as with H1N1 have shown us that immune systems are quite different in very sex-specific ways. I think the difference in COVID-19 outcomes between the sexes will probably turn out to be related to that.

Libby: The socioeconomic and racial disparities in who is getting and dying from this disease are glaring. It's very upsetting.

Bairey Merz: I wonder if the racial disparities that have emerged are somehow related to how RAAS {Renin-Angiotensin-Aldosterone System} inhibitors are not as effective in African American patients as they are in Caucasian patients. The coronavirus gets into the cell using ACE2. I can imagine that African American patients on average may have some difficulties in their immune function that would be special to this coronavirus.

Arrhythmia risks of potential treatments

Pepine: At our institution, every patient with COVID-19 now gets hydroxychloroquine and azithromycin, both of which can prolong the QT interval. Dr. Woosley, can you discuss these concerns?

Raymond L. Woosley, MD, PhD: In March, there were two online reports of uncontrolled observations in small numbers of patients with COVID-19 treated with hydroxychloroquine, sometimes combined with azithromycin, that got a lot of attention in the lay press. Subsequently, there have been concerns voiced about their lack of adequate controls and analysis of data. The evidence for the efficacy of these antimalarials for the treatment of COVID-19 is anecdotal at best. At this time, we don't have credible evidence that any drug has clinical benefit, so it is essential that we anticipate and manage their potential risks.

Because of these trials, on March 28, the FDA issued an emergency use authorization (EUA) for hydroxychloroquine and chloroquine as treatment for adults and adolescents who are hospitalized for COVID-19 and for whom a clinical trial is not available. Unfortunately, many misinterpreted this EUA as "FDA approval" and the uncontrolled use of these drugs exploded. This widespread use in outpatients and even for COVID-19 prophylaxis led the FDA to issue a warning on April 24 to caution against use of the drugs in outpatients or outside of clinical trials due to the risk for cardiac arrhythmias including ventricular tachycardia/torsades de pointes. The warning strongly discouraged use of the drugs with azithromycin or other drugs that prolong QT. It also mentioned that these arrhythmias are more likely to occur in patients with cardiac risk factors frequently seen in patients with COVID-19. I encourage anyone considering prescribing these drugs for COVID-19 to try to enroll their patients in a trial and if that is not feasible, carefully read the FDA's fact sheet.

The FDA's EUA and the drug labels for hydroxychloroquine and chloroquine contain two important warnings for prescribers. The first is to discontinue any nonessential drugs that prolong QT. This requires that the patient's drug list be screened for any of the 145 other drugs that are known to prolong QT. The second recommendation is to identify and, if possible, mitigate risk factors for QT prolongation such as hypokalemia and sepsis. Obviously, compliance with these recommendations is not simple and would require decision support programs that are not available in every hospital.

The Arizona Center for Education and Research on Therapeutics, a nonprofit which I lead, recently launched a web-based program, www.MedSafetyScan.org, that screens patients for risk factors and QT-prolonging drugs. It can be used if you don't have a decision support system operating in your hospital electronic medical record to manage QT risk.

It would be great if hydroxychloroquine and chloroquine were in fact helping patients with COVID-19. But without controlled trials, we will never be sure and will not know the serious harm they may be causing.

Pepine: Is your institution using hydroxychloroquine?

Mehra: We are studying it, of course, but not in a randomized manner.

Woosley: About 30% of the patients with COVID-19 in our hospital were being treated with hydroxychloroquine and many of those also received azithromycin. With the new FDA warning, prescription of hydroxychloroquine is now being discouraged and can no longer be prescribed for any outpatients with COVID-19 or for most inpatients. I

hear from pharmacies in the community that it is still being prescribed, but patients with arthritis and lupus are having difficulty filling their prescriptions.

Pepine: Ours is much higher. It's hard to find a patient without it.

Take-home messages

Pepine: What are your take-home messages?

Raizada: Is it possible to find a way to make some kind of decoy to "soak up" circulating viral particles to clear up the infection more rapidly? We have been thinking about using a probiotic approach which has ACE2-soluble ACE2 or secreted ACE2.

Bohula: We are in the very early stages of thinking about therapeutics for COVID-19. We have many potential options based on what we know about how this virus works, and about what we believe to be a secondary hyper-inflammatory state. But we need data and I unfortunately don't think we have good data yet to support any specific therapies at this time. With collaborative efforts, we'll get to the answer at some point. We are moving in the right direction.

Jaffe: For many years, troponin has been viewed as just a marker of MI. It's time to move beyond that. That's the only way to be able to cautiously and appropriately interpret values. It's a great time to understand that troponin is your friend. Clinically, following troponin trends and the BNP trends and using them cautiously to define when additional testing may be helpful is where I predict the field will evolve.

Libby: One point is the absolute necessity of randomized clinical trials before we jump on the bandwagon for any therapies. A list of selected ongoing trials is in Table 1 on page 12. This disease is a paradise for clinical trials because you have lots of endpoints and they accrue quickly. We have equipoise {a state of equilibrium}, so there shouldn't be any hesitation to enroll patients. We all have an ethical responsibility to contribute to research that is going to fill in the blanks because we have a crying clinical need and we have an enormous opportunity to garner some data at warp speed that will give us a evidence base so we can rationally treat these patients. We have to avoid the idea of "what have you got to lose?"

Mehra: COVID-19 is as much a CV disease as it is a pulmonary disease. We need to focus our research efforts directly on trying to understand the various phenotypes of presentation of what we can now call "acute COVID cardiovascular dysfunction." We need to diagnose the cardiomyopathy early and push to use and preserve medications such as ACE inhibitors and statins that have been shown to be very important, not only as endothelial stabilizing drugs, but as anti-inflammatory drugs and also neuro-hormonally active drugs.

Moslehi: Using a playbook from the oncology and immunology space, we have to understand better whether this is truly a myocarditis syndrome in the classic sense, or something indirect as a result of activation of T cells, perhaps mimicking the cytokine release syndrome we see with CAR T-cell therapy. To understand that better, I think pathological examination would be important. In recent years, there has also been an explosion of new tools in immunology and molecular biology. It is time for us cardiologists to take advantage of these to ask questions.

Woosley: This discussion has covered numerous examples of how biomedical science at all levels can help us understand the pathophysiology of a new, never-before seen illness and develop testable hypotheses for its diagnosis, management and treatment. Our success in finding effective modes of treatment and prevention will require rigorous, controlled clinical investigations that are based on the best scientific rationale we can muster.

Bairey Merz: Stay safe. It's important to keep the health care providers healthy enough so we can take care of the sick patients. We are learning a lot, like from our younger doctors who are doing preround telehealth and then deciding who is critically ill enough to be seen face to face. Our institution has done a very good job of preventive intubation, meaning we do not wait until it's an emergency, and using shielding technology to "seal off " the patient from the anesthesiologist, the respiratory therapist and the intensivist, for example.

Pepine: Clearly, our knowledge of this novel coronavirus and its CV complications is evolving by the hour. We believe that it's critical for the medical community, particularly the community on the front lines, at the time of this pandemic to share knowledge on this. So let's all keep safe, and I'll probably see you at a face-to-face meeting this year when this pandemic

is over. compiled by Katie Kalvaitis, with additional editing by Erik Swain I

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