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ABSTRACT

# Report of the British Society for Cardiovascular Research Inaugural Online Autumn Meeting 2020

Helen M. Arthur[1*]
[1]Biosciences Institute, Centre for Life, Newcastle University, Newcastle NE1 3BZ, UK

The British Society for Cardiovascular Research (BSCR; https://bscr.org) postponed its regular autumn meeting until September 2021 due to the COVID-19 pandemic. This also meant that the annual Bernard and Joan Marshall Early Career Investigator Award, which forms an important part of the autumn meeting, also had to be postponed. However, in order to provide an online BSCR meeting forum this autumn, the BSCR organised a highly topical online mini-symposium on 8th September 2020 entitled "Coronavirus and the cardiovascular system". This online meeting was free to attend and was open to BSCR members and non-members. Altogether, there were 174 attendees, including some from outside the UK. The feedback was very positive, and a recording is available for part of the meeting on the BSCR webpage (https://bscr.org/event/bscr-autumn-2020-ol/).

The audience was warmly welcomed by the BSCR committee chair, Dr Karen Porter, from the University of Leeds, and then, three excellent speakers presented on complementary aspects of COVID-19 and the cardiovascular system. Dr Mairi Brittan (University of Edinburgh) introduced the first speaker Dr Anda Bularga, a clinical research PhD student supervised by Professors Nicholas Mills and David Newby in the BHF Centre for Cardiovascular Science at the University of Edinburgh. In her talk entitled "COVID-HEART: Direct and indirect effects of COVID-19 on acute cardiac care", Dr Bularga outlined how COVID-19 disease begins in the respiratory system, with breathlessness as the most common presenting symptom. Chronic heart disease and diabetes are common co-morbidities in hospitalised COVID-19 patients, and research so far has shown that these patients are at higher risk of adverse clinical outcomes. A considerable research effort is underway to improve our understanding of this condition.

Biomarkers for myocardial injury provide a useful way of tracking injury and risk. These include troponin (Tn) I released from injured cardiomyocytes and BNP released in response to myocardial stretch. COVID-19 patients with increased TnI blood levels have a significantly increased risk of mortality. The underlying mechanism of myocardial injury in the majority of these patients remains uncertain. Early clinical experience and case reports identified a number of well-recognised clinical conditions in patients with COVID-19 including acute viral myocarditis, stress or Takotsubo cardiomyopathy and thromboembolic disease. In recently published work [1], Dr Bulgara and the team at the University of Edinburgh collaborated with the European Association of Cardiovascular Imaging to examine echocardiographic data to evaluate cardiac abnormalities in 1216 COVID-19 patients from 69 countries. Of these patients, 55% had an abnormal echocardiogram with a range of cardiac phenotypes affecting left, right or both ventricles. Elevated blood troponin and BNP were independent predictors of abnormal left ventricular function, whilst increased severe respiratory symptoms were associated with an abnormal right ventricle. The pathobiology of myocardial injury post-COVID-19 infection appears to be diverse and complex and is an ongoing area of active investigation.

Dr Bularga also discussed recent reports of a worldwide reduction in patients attending hospital with heart attacks. In England, there was almost a 50% decrease in heart attack patients during the peak of the pandemic when compared with a calendar-matched period in previous years. A patient-centred telephone interview study suggested that anxiety around the risk of COVID-19 infection was an important factor. Any patient with untreated myocardial infarction will inevitably incur increased myocardial damage that is likely to lead to an increased risk of cardiac problems such as heart failure in the next months and years.

Dr Sanjay Sinha (University of Cambridge) introduced our next speaker

Professor Anthony Davenport (Professor of Cardiovascular Pharmacology, Addenbrookes Hospital, University of Cambridge). His talk was entitled "ACE2, the viral entry 'receptor' for SARS-CoV-2 in the human cardiovascular system". The theme running through this talk was ongoing work to test existing medicines for their ability to disrupt COVID-19 cellular entry. Currently available medicines (e.g. see the open drug database IUPHAR) would have the potential for rapid repurposing to target COVID-19 where there is an appropriate drug target with supportive evidence.

Early data from 45,000 COVID-19 patients in China showed that age (>70-year case fatality rate (CFR) 10%), cardiovascular disease (CFR 10%) and hypertension (CFR 6%) are independent predictors of adverse outcomes. Although the primary site of infection is the lung tissue, evidence of myocardial injury in COVID-19 patients suggests that viral infection of cardiomyocytes may also be involved.

ACE2 protein is used by COVID-19 to gain cell entry. It is a transmembrane peptidase with a cardiovascular protective role. It is perhaps best known for converting the vasoconstrictor peptide angiotensin II to the vasodilator peptide angiotensin (1-7). ACE2 also inactivates the pro-inflammatory peptide des-Arg9-bradykinin and generates the vasodilator Pyr1apelin-13 (1-12). These protective roles of ACE2 may be disrupted by COVID-19 infection. ACE2 is expressed on barrier cells including lung epithelium, endothelial cells and enterocytes of the small intestine, and COVID-19 infection also disrupts this barrier function.

Although COVID-19 viral entry depends on interaction with ACE2 on the cell surface, additional proteins are required. In particular, the serine protease TMPRSS2 is required to cleave and thereby activate the viral Spike protein, whilst the endosomal cysteine proteases cathepsin B and L can also promote viral entry into the cell. Another protein known as BOAT1 (or SLC6A18), an amino acid transporter complex, may have an ancillary role in promoting viral entry. Furthermore, the protease FURIN can cleave the spike protein of new viral particles generated within the cell that may facilitate their entry into new host cells. Because these six proteins are important for viral entry/processing, they also represent potential drug targets to disrupt viral entry. Some drugs are already available in the clinic that target these proteins. For example, camostat is a potent serine protease inhibitor that targets TMPRSS2 and is used to treat some forms of cancer but is now in clinical trials to assess whether it can provide any protection from COVID-19 infection. In addition, the extracellular ACE2 domain can be cleaved from the cell surface by the metalloproteinase ADAM17, and soluble ACE2 may bind the viral spike protein to act as a viral decoy preventing cell entry. Recombinant human soluble ACE2 (APN01) is in phase 2 clinical trials to treat COVID-19.

Building on these findings, Professor Davenport asked whether this group of viral entry/processing genes is differentially expressed (i) between young and aged cardiomyocytes, and (ii) between healthy hearts and those with dilated cardiomyopathy (DCM). To address the first of these questions, single nuclear (sn) RNA was collected post-mortem from left ventricular cardiomyocytes of 5 old (63–78 years) and 5 young (19–25 years) males without cardiovascular disease and without medication. Analysis of snRNAseq data showed increased expression of the viral entry genes in old compared with young cardiomyocytes that could explain a potential increased vulnerability of older patients to cardiac complications [2]. To determine expression changes in the viral entry/processing genes in DCM, bulk RNAseq analysis of left ventricle tissue was used to compare the transcriptomes of 7 male DCM patients (undergoing transplantation) with 5 controls. Transcript analysis showed increased expression of some of these viral entry genes in explanted DCM hearts.

To complement this work, cardiac expression of viral entry/processing proteins was validated using immunofluorescence staining in tissue sections of left ventricles from heart transplant patients with cardiomyopathy. Coronary vessels and cardiomyocytes showed presence of viral entry proteins. A key subsequent question was whether these viral entry/processing genes are also expressed in human embryonic stem cell derived cardiomyocytes (hESC-CM), and this expression was confirmed at both transcript and protein level. Therefore, hESC-CM provide a valuable tool for investigating novel therapeutic drugs that inhibit viral entry.

Dr Sarah Withers (University of Salford) introduced our final speaker Professor Tomasz Guzik (Regius Professor of Physiology, University of Glasgow). His presentation entitled "Immunopathology of cardiovascular disease as contributor to greater risk of COVID-19" began with a reminder that the main cause of death in COVID-19 patients is acute respiratory distress syndrome (ARDS). There are many observational studies suggesting correlations between COVID-19 disease severity and hypertension and diabetes, whilst increased age is the strongest predictor of the severe course of COVID-19. Notably, hypertensive disease but not hypertensive treatment (using ACE inhibitors or angiotensin receptor blockers) increases mortality risk. In fact, anti-hypertension drugs and renin-angiotensin-aldosterone system (RAAS) inhibitors appear to be beneficial for COVID-19 patients with hypertensive disease [3].

A cytokine storm is characteristic of patients with severe COVID-19 disease. Two recent studies showed that hospitalized COVID-19 patients with severe disease had different patterns of lymphocyte responses [4, 5]. Rapid deterioration in COVID-19 patients is associated with reduced lymphocyte blood counts, but those T cells that are present show increased activation with particular increase in cytotoxic $CD8^+$ cells and proliferating effector memory cells. In severe COVID-19 patients, there are also increased circulating levels of pro-inflammatory cytokines (e.g. IL-6 and IL-8), and chemokine IP-10 (CX3CL10) levels seem particularly strongly correlated with disease severity. Endothelial dysfunction in severe COVID-19 disease may be an indirect outcome of the cytokine storm

Hypertensive patients fall into three different groups based on their levels of pro-inflammatory cytokines. Those hypertensive patients with increased pro-inflammatory cytokines may be predisposed to more severe disease due to dysregulation of the immune system. Mice treated with angiotensin II provide an established model of hypertension. Angiotensin II infusion leads to an altered immunophenotype, and there are increased numbers of T cells, B cells, macrophages and dendritic cells associated with the vasculature. Using confocal imaging of the vessel wall, T cells are seen actively moving within the perivascular space.

scRNAseq analysis of immune cells in the blood vessel wall in mice showed lack of ACE2/TMPRSS2 expression, suggesting that the effects of COVID-19 on these immune cells are indirect. This finding is in line with findings from scRNAseq analysis of human heart tissue showing that ACE2 is primarily expressed in pericytes, with some cardiomyocyte expression, but is not detected in immune cells [6].

RAG1 null mice and rats have no mature lymphocytes and are protected from angiotensin II induced hypertension pointing to a role of lymphocytes in the hypertensive response. In hypertensive patients circulating memory and effector (Th17), T cells are increased compared with controls [7]. Using Biobank data, Professor Guzik found that numbers of circulating lymphocytes, monocytes and neutrophils were higher in individuals with increased blood pressure. Using Mendelian randomisation techniques, further analysis suggests that increased lymphocytes are causally related to increased blood pressure, whilst increased monocytes and neutrophils occur in response to increased blood pressure [8]. Hypertensive patients also have increased numbers of T cells in the vessel wall of coronary arteries. Furthermore, the presence of increased numbers of $CD8^+$ cells is associated with endothelial dysfunction perhaps in response to their production of inflammatory cytokines. In support of this hypothesis, vessels with high numbers of $CD8^+$ T cells in the vessel wall also show increased expression of inflammatory cytokines such as CCL5 and TNFα. In addition, TNFα and IFNγ are expressed by $CD8^+$ cells obtained from perivascular adipose tissue.

A particular group of T cells ($CD8^+$ $CD28^-$) increase with age and correlate positively with blood pressure and negatively with endothelial cell function. It will be of interest to look at any association of these cells with COVID-19 disease outcomes. In conclusion, Professor Guzik considered that pre-activation of the immune system in hypertension may play a role in predisposition to severe COVID-19 disease, and this is an area of ongoing investigation.

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