COVID-19 infection ECG: (a) biphasic T waves; (b) reduction in T wave amplitude by 50% in contiguous leads; (c) ST segment depression; (d) J-point and ST segment elevation > 0.2 mV in the precordial leads and >0.1 mV in the limb leads; (e) tall T waves ≥ 1.0 mV (f) low QRS amplitude in > 3 limb leads and (g) complete right bundle branch block. Athletes exhibiting novel ECG changes underwent cardiovascular magnetic resonance (CMR) scans. One club mandated CMR scans for all 28 (6%) athletes, despite the absence of cardiac symptoms or ECG changes.

**Results** Athletes were aged 22 ± 5 years, 89% were male and 57% were white, 65 (14%) athletes reported cardiac symptoms. The mean duration of illness was 3 ± 4 days. The post COVID ECG was performed 14 ± 16 days following a positive PCR test. 440 (97%) athletes had an unchanged post COVID-19 ECG. Of these, 3 (0.6%) had cardiac symptoms and CMRs resulted in a diagnosis of pericarditis. 15 (3%) athletes demonstrated novel ECG changes following COVID-19 infection. Among athletes who demonstrated novel ECG changes, 10 (67%) reported cardiac symptoms. 13 (87%) athletes with novel ECG changes were diagnosed with inflammatory cardiac sequelae; pericarditis (n=6), healed myocarditis (n=3), definitive myocarditis (n=2), and possible/probable myocarditis (n=2). The overall prevalence of inflammatory cardiac sequelae in the cohort based on novel ECG changes was 2.8%.

None of the 28 (6%) athletes, who underwent a CMR, in the absence of cardiac symptoms or novel ECG changes revealed any abnormalities. Athletes revealing novel ECG changes, had a higher prevalence of cardiac symptoms (67% vs 12% p<0.0001) and longer symptom duration (8±8 days vs 2±4 days; p<0.0001) compared with athletes without novel ECG changes. Among athletes without cardiac symptoms, the additional yield of novel ECG changes to detect cardiac inflammation was 20% (n=3).

**Conclusions** 3% of elite soccer players demonstrated novel ECG changes post COVID-19 infection, of which almost 90% were diagnosed with cardiac inflammation during subsequent investigation. Most athletes with novel ECG changes exhibited cardiac symptoms. Novel ECGs changes contributed to a diagnosis of cardiac inflammation in 20% of athletes without cardiac symptoms.

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**A MULTI-OMICS APPROACH TO GENERATE NOVEL MECHANISTIC INSIGHTS AND NEW TARGETS FOR CARDIOVASCULAR REGENERATION IN THE ISCHAEMIC ADULT HEART**

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**Background** Myocardial infarction (MI) is the leading cause of heart failure. The adult human heart, unlike mouse or early neonatal hearts, lacks the capability to undergo extensive regeneration. Rapid re-establishment of blood flow post MI is vital for limiting tissue damage and preserving cardiac function. A better understanding of the mechanisms underpinning cardiovascular regeneration in adult hearts is needed. Recent technologies including single cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) have empowered studies of healthy and diseased tissue at unprecedented resolution.

**Methods and Results** First, we established an EC-specific multispectral lineage-tracing mouse model (Pdgfb-iCreERT2-R26R-Brainbow2.1) and assessed EC clonal proliferation in the adult heart post MI. We discovered a significant increase in clone size in the MI hearts compared to the healthy controls (cells per clone = 4.0 ± 2.1 vs. 10.3 ± 10.6, P < 0.0001), demonstrating that the structural integrity of adult endothelium following MI was maintained through clonal proliferation by resident ECs in the infarct border region. We then isolated the Pdgfb-lineage ECs from the healthy (12,780) and injured (15,818) hearts through FACS, performed scRNA-seq and downstream analysis, and defined ten transcriptionally discrete heterogeneous EC states and associated pathways that might impact upon cardiovascular regeneration. Next, high-quality scRNA-seq data from 10 curated studies of the mouse and human hearts were integrated for a cross-species systematic meta-analysis. Coronary ECs were enriched in silico based on the expression of 45 endothelial markers and analysed using Seurat. Unsupervised clustering of integrated neonatal and adult mouse coronary ECs revealed 15 transcriptionally distinct clusters. The subsequent DEG analysis identified the Vegfc pathway as a program that can potentially augment adult cardiovascular regeneration in the neonatal heart. The integration of the mouse and human coronary EC data and the DEG analysis identified 41 commonly upregulated genes after ischaemic injuries, including KLF4, EGR1 and ZFP36. Further, spatial transcriptomics analysis of MI patient-derived heart tissues revealed the elevation of these conserved targets in the damaged tissues in the acute phase. We validated the upregulation of these targets in the injured human coronary ECs (% KLF4+ CD31+ EC = 29.7 ± 7.5% versus 7.3 ± 6.4%, P = 0.0009, % EGR1+ CD31+ EC = 10.1 ± 3.5% versus 3.4 ± 2.5%, P = 0.004; ZFP36 expression was high the diseased tissue but minimal in control hearts). In vitro siRNA knockdown of ZFP36 in cultured human cardiac microvascular endothelial cells (HCMECs) showed that cell proliferation was significantly inhibited compared to the control siRNA treatment (Fold change of % EdU+ HCMECs = 0.84 ± 0.19 vs 0.25 ± 0.12, P = 0.0007). In vivo, we used the multi-spectral MI mouse model and showed that the administration of rhVEGF-C significantly increased neovascularisation in the infarct border in the adult mouse heart compared to the PBS treated controls (vascular clone volume (μm^3) = 3072 ± 491.2 versus 426 ± 105, P = 0.02).

**Conclusion** We have successfully developed and implemented a robust framework, using meta-analysis of scRNA-seq, spatial transcriptomics, tissue section immunofluorescence, primary human cell culture, and multispectral MI mouse model, to collectively identify, assess, and validate novel mechanisms and targets potential to promote vascular regeneration.