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SCVP Journal Club 11/22/2022

Original articles for discussion

1. Lim MS, Portelli SS, Padang R, et al. Novel insights into bicuspid aortic valve (BAV) aortopathy: Long non-coding RNAs TUG1 and MIAT are differentially expressed in BAV ascending aortas. *Cardiovasc Pathol*. 2022;60:107433. doi:10.1016/j.carpath.2022.107433
Background: The underlying pathogenesis of bicuspid aortic valve (BAV) aortopathy is unclear.
Methods: Expression of 28 lncRNA by RT-qPCR from BAV aortas (n=29) were compared with normal control (n=7).
Result and conclusion: *TUG1* expression was significantly lower in BAV and *MIAT* expression was significantly higher.

2. Jum'ah H, Kundrapu S, Jabri A, Kondapaneni M, Tomashefski JF, Loeffler AG. Cardiac macrophage density in Covid-19 infection: relationship to myocyte necrosis and acute lung injury. *Cardiovasc Pathol*. 2022;60:107447. doi:10.1016/j.carpath.2022.107447
Background: COVID19 patients can have cardiac involvement with morbidity and mortality.
Methods: Ten COVID19 decadents and 20 non-COVID19 pneumonia/DAD decedents was utilized to study single myocyte necrosis and macrophages distribution in the setting of acute lung injury.
Result and conclusion: No lymphocytic myocarditis was identified. Single myocyte necrosis is more common in the COVID19 group. The density of macrophages is highest COVID19 with necrosis group, followed by COVID19 without necrosis then control.

3. Mutagaywa RK, Mwakigonja A, Chillo P, et al. Histopathological evaluation of chronic rheumatic mitral valve stenosis: the association with clinical presentation, pathogenesis, and management at a National Cardiac Institute, Tanzania. *Cardiovasc Pathol*. 2022;60:107434. doi:10.1016/j.carpath.2022.107434
Background: It is known that patients with rheumatic fever can have mitral valve pathology, mostly from case report or limited case series.
Methods: Prospective study of 54 rheumatic stenotic mitral valves using HE stain, von Kossa stain and IHC (CD3, CD20, CD68 and CD8) was performed.
Result and conclusion: High calcium deposit was found in patients with older age, male and severe stenosis (not statistically significant). Inflammatory infiltrates are associated with calcifications.

4. Shah P, Agbor-Enoh S, Bagchi P, et al. Circulating microRNAs in cellular and antibody-mediated heart transplant rejection. *J Heart Lung Transplant*. 2022;41(10):1401-1413. doi:10.1016/j.healun.2022.06.019
Background: MicroRNAs (miRs) is a promising biomarkers for a noninvasive cardiac allograft surveillance.
Methods: A miR panel was developed comparing profiling between patients without rejection versus patients with ACR and/or AMR in The Genomic Research Alliance for Transplantation (GRAfT) cohort (108 controls and 49 with rejection (50 ACR >=2R and 38 AMR episodes)), then validated in an independent cohort.

Result and conclusion: 12 miRs can accurately discriminate ACR and 17 miRs for AMR. The validation cohort showed ACR AUC 0.92 and AMR AUC 0.82. Clinical ACR and AMR miR clinical scores were developed based on the data.

5. Eichenberger EM, Coniglio AC, Milano C, et al. Transplanting thoracic COVID-19 positive donors: An institutional protocol and report of the first 14 cases. *J Heart Lung Transplant*. 2022;41(10):1376-1381. doi:10.1016/j.healun.2022.06.018
Background: During pandemic, donors might be COVID19 positive.
Methods: Reporting institutional experience of 12 hearts and 2 sets of lung from COVID19-positive donor. Median follow-up: 215 days.
Result and conclusion: No unexpected acute cellular rejection, with 92% patient survival. No recipient developed COVID19 symptoms. One patient retransplanted on D6 due to hemorrhage and hypercoagulability. One patient died on D88 due to aortic anastomosis breakdown and Rhizopus mediastinitis.

6. Cardoso B, Wang J, Kiernan J, Dipchand AI. Eplet matching in pediatric heart transplantation: The SickKids experience. *J Heart Lung Transplant*. 2022;41(10):1470-1477. doi:10.1016/j.healun.2022.06.023
Background: Epitope-based tissue matching may be superior to traditional HLA antigen matching, and preventing DSA formation.
Methods: Single-center retrospective study of 77 pediatric patients with HLA typing, antigen mismatch, and eplet mismatch analysis. HLAMatchmaker software (HLAMatchmaker DRDQDP Matching v 3.1) was used to identify the eplet mismatches between each donor and recipient.
Result and conclusion: HLA Class II DPB eplet mismatches is associated with graft loss; HLA eplet mismatching was not associated with rejection; antigen mismatching was not associated with graft loss or rejection.

7. Mehdiabadi NR, Boon Sim C, Phipson B, et al. Defining the Fetal Gene Program at Single-Cell Resolution in Pediatric Dilated Cardiomyopathy. *Circulation*. 2022;146(14):1105-1108. doi:10.1161/CIRCULATIONAHA.121.057763
Background: Previous literature suggests postnatal heart exhibit “fetal-like” gene expression profile when stressed.
Method: snRseq was performed using fetal, non-diseased, and early-onset DCM human hearts (n=3-4)
Result and conclusion: Reactivation of fetal genes was found in DCM cardiomyocytes and fibroblasts (~8% fetal genes).

8. Lota AS, Hazebroek MR, Theotokis P, et al. Genetic Architecture of Acute Myocarditis and the Overlap With Inherited Cardiomyopathy. *Circulation*. 2022;146(15):1123-1134. doi:10.1161/CIRCULATIONAHA.121.058457
Background: Acute myocarditis might trigger subsequent DCM and or ACM (arrhythmogenic cardiomyopathy).

Methods: 336 consecutive myocarditis patients with targeted DNA sequence of known cardiomyopathy genes (11 DCM [*BAG3, DES, LMNA, MYH7, PLN, RMB20, SNC5A, TNNC1, TNNT2, TPM1, and TTN*] and 5 ACM [*DSC2 DSG2, DSP, PKP2, and JUP*]) and compared with healthy controls.
Result and conclusion: In myocarditis cohort, 8% patients have pathogenic DCM/ACM variants (control: <1%). The 5-year mortality risk was 3.3% in genotype-negative patients versus 11.1% in genotype-positive patients (p=0.08). *DSP* and *TTN* truncation variants were enriched.

Notable article

1. Gupalo EM, Buryachkovskaya LI, Chumachenko PV, et al. Implication of inflammation on Coxsackie virus and Adenovirus receptor expression on cardiomyocytes and the role of platelets in patients with dilated cardiomyopathy. *Cardiovasc Pathol*. 2022;60:107452. doi:10.1016/j.carpath.2022.107452
Background: The Coxsackie virus and Adenovirus receptor (CAR) may play roles in the pathogenesis of inflammatory DCM, with limited data in human regarding CAR, platelets (which express CAR) in myocarditis and DCM.
Methods: EMBs, platelets, and serum levels of TNF-alpha/IL-6 from 38 DCM patients were studied. Platelets and serums from healthy controls (n=20) were also studied.
Result and conclusion: Platelet CAR expression is higher in DCM than controls. CAR expression in EMB and platelets are associated with higher inflammatory signatures in serum.

2. Kapadia SR, Makkar R, Leon M, et al. Cerebral Embolic Protection during Transcatheter Aortic-Valve Replacement. *N Engl J Med*. 2022;387(14):1253-1263. doi:10.1056/NEJMoa2204961
Background: Transcatheter aortic-valve replacement (TAVR) can cause embolization.
Methods: Randomized clinical trial for 3000 TAVR patients with or without cerebral embolic protection (CEP).
Result and conclusion: Incidence of stroke within 72 hours or before discharge did not different between two groups.

3. Perera D, Clayton T, O'Kane PD, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. *N Engl J Med*. 2022;387(15):1351-1360. doi:10.1056/NEJMoa2206606
Background: The benefit of PCI (percutaneous coronary intervention) for ICM (ischemic cardiomyopathy) patient is unclear.
Methods: Randomized clinical trial for 700 ICM patient for PCI versus optimal medical therapy. (medium follow-up: 41 months)
Result and conclusion: No difference in primary outcome (death or hospitalization) or secondary outcome (LVEF and quality of life scores at month 6 and 12).

4. Lindholt JS, Søgaard R, Rasmussen LM, et al. Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial. *N Engl J Med*. 2022;387(15):1385-1394. doi:10.1056/NEJMoa2208681
Background: Population-based cardiovascular disease screening might be beneficial.

Methods: 46611 men (65-75 yo) randomized into screening versus not in 1:2 ratio. The screens includes non-contrast CT, BP measurement, and blood test. Primary outcome as death. (medium follow-up: 5.6 years)
Result and conclusion: No difference in primary outcome.

5. Mackenzie IS, Rogers A, Poulter NR, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial. Lancet. 2022;400(10361):1417-1425. doi:10.1016/S0140-6736(22)01786-X
Background: Prior literature suggests bedtime antihypertensive medication might have better outcome compared with morning dosing.
Methods: 21104 participants in UK randomly assigned to morning versus evening dosing group. Composite primary endpoint: vascular death or hospitalization for non-fatal myocardial infarction or non-fatal stroke. (median follow-up:5.2 years)
Result and conclusion: No difference in primary outcome.

6. Mackenzie IS, Hawkey CJ, Ford I, et al. Allopurinol versus usual care in UK patients with ischaemic heart disease (ALL-HEART): a multicentre, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10359):1195-1205. doi:10.1016/S0140-6736(22)01657-9
Background: Previous study suggests allopurinol might be beneficial for cardiovascular outcome.
Methods: 5721 ICM participants (aged 60 years or older without gout) randomized into allopurinol groups versus usual care. Primary outcome was composite non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. (median follow-up:4.8 years)
Result and conclusion: No difference in primary outcome.

7. de Frutos F, Ochoa JP, Navarro-Peñalver M, et al. Natural History of MYH7-Related Dilated Cardiomyopathy. *J Am Coll Cardiol*. 2022;80(15):1447-1461. doi:10.1016/j.jacc.2022.07.023
Background: *MYH7* mutations can cause DCM but the phenotype, prognosis and correlation with genotype is largely unknown.
Methods: 147 individuals with DCM-causing *MYH7* variants were included in this study. (medium follow-up: 4.5 years)
Result and conclusion (72.1%) patients had DCM when enrolled, and 23.7% of carriers who were initially phenotype-negative developed DCM during the study. *MYH7*-related DCM is characterized by early age of onset, high phenotypic expression, low left ventricular reverse remodeling, and frequent progression to end-stage heart failure.

Others publications (potential of interest but not reviewed)

1. Lacaze P, Bakshi A, Riaz M, et al. Aspirin for Primary Prevention of Cardiovascular Events in Relation to Lipoprotein(a) Genotypes. *J Am Coll Cardiol*. 2022;80(14):1287-1298. doi:10.1016/j.jacc.2022.07.027

2. Cunningham JW, Vaduganathan M, Claggett BL, et al. Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection Fraction. *J Am Coll Cardiol*. 2022;80(14):1302-1310. doi:10.1016/j.jacc.2022.07.021
3. Böhme M, Desch S, Rosolowski M, et al. Impact of Clonal Hematopoiesis in Patients With Cardiogenic Shock Complicating Acute Myocardial Infarction. *J Am Coll Cardiol*. 2022;80(16):1545-1556. doi:10.1016/j.jacc.2022.08.740
4. Andreasen L, Ahlberg G, Ægisdottir HM, et al. Genetic Variants Close to *TTN*, *NKX2-5*, and *MYH6* Associate With AVNRT. *Circ Res*. 2022;131(10):862-865. doi:10.1161/CIRCRESAHA.122.321556
5. Butt JH, Jhund PS, Belohlávek J, et al. Efficacy and Safety of Dapagliflozin According to Frailty in Patients With Heart Failure: A Prespecified Analysis of the DELIVER Trial. *Circulation*. 2022;146(16):1210-1224. doi:10.1161/CIRCULATIONAHA.122.061754
6. Thibord F, Klarin D, Brody JA, et al. Cross-Ancestry Investigation of Venous Thromboembolism Genomic Predictors. *Circulation*. 2022;146(16):1225-1242. doi:10.1161/CIRCULATIONAHA.122.059675
7. Pagano F, Picchio V, Bordin A, et al. Progressive stages of dysmetabolism are associated with impaired biological features of human cardiac stromal cells mediated by the oxidative state and autophagy. *J Pathol*. 2022;258(2):136-148. doi:10.1002/path.5985

Review, consensus, statement

1. Basso C. Myocarditis. *N Engl J Med*. 2022;387(16):1488-1500. doi:10.1056/NEJMra2114478
2. Singh TP, Cherikh WS, Hsich E, et al. The International thoracic organ transplant registry of the international society for heart and lung transplantation: Twenty-fifth pediatric heart transplantation report-2022; focus on infant heart transplantation. *J Heart Lung Transplant*. 2022;41(10):1357-1365. doi:10.1016/j.healun.2022.07.019
3. Hsich E, Singh TP, Cherikh WS, et al. The International thoracic organ transplant registry of the international society for heart and lung transplantation: Thirty-ninth adult heart transplantation report-2022; focus on transplant for restrictive heart disease. *J Heart Lung Transplant*. 2022;41(10):1366-1375. doi:10.1016/j.healun.2022.07.018
4. Tseliou E, Lavine KJ, Wever-Pinzon O, et al. Biology of myocardial recovery in advanced heart failure with long-term mechanical support. J Heart Lung Transplant. 2022;41(10):1309-1323. doi:10.1016/j.healun.2022.07.007
5. Januszewicz A, Mulatero P, Dobrowolski P, et al. Cardiac Phenotypes in Secondary Hypertension: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2022;80(15):1480-1497. doi:10.1016/j.jacc.2022.08.714

Case Reports

1. Monteagudo-Vela M, Rosell Alayza A, Monguió Santín E, Cecconi A, Reyes Copa G. Pulmonary artery sarcoma with extensive leiomyosarcoma differentiation and heterologous osteosarcomatous elements. *Cardiovasc Pathol*. 2022;60:107436. doi:10.1016/j.carpath.2022.107436

2. Nakatani S, Ohta-Ogo K, Nishio M, et al. Microthrombosis as a cause of fulminant myocarditis-like presentation with COVID-19 proven by endomyocardial biopsy. *Cardiovasc Pathol*. 2022;60:107435. doi:10.1016/j.carpath.2022.107435
3. Cirino Ballantyne M, Chiu B, Sergi CM. Sanfilippo syndrome type A: early cardiac involvement of two patients with cardiac manifestations. *Cardiovasc Pathol*. 2022;60:107430. doi:10.1016/j.carpath.2022.107430
4. Zheng YJ, Ren L, Zhu Y, et al. DICER1-associated sarcoma of the aortic arch - a case report and literature review. *Cardiovasc Pathol*. 2022;60:107451. doi:10.1016/j.carpath.2022.107451
5. Kanamori H, Yoshida A, Sasai H, Miyazaki T, Mikami A, Okura H. A case of endomyocardial biopsy-proven early stage cardiac involvement in heterozygous Fabry disease. *Cardiovasc Pathol*. 2022;60:107453. doi:10.1016/j.carpath.2022.107453
6. Denu RA, Solomon DH, Mitchell RN, Sun YP, Loscalzo J. Thinking Outside the Heart. *N Engl J Med*. 2022;387(14):1310-1316. doi:10.1056/NEJMcps2206178 (eosinophilic granulomatosis with polyangiitis)
7. Rebello A, Joshi P. Giant-Cell Arteritis. *N Engl J Med*. 2022;387(15):e36. doi:10.1056/NEJMicm2202567