Children's Foundation Research Institute

Research Matters

Summer 2021

Competition after COVID-19

Cardiologists show heart damage in athletes unlikely after COVID-19 infection

Le Bonheur's Sports Cardiology team (left to right) Ryan E. Stephens, NP-C, MBA, Jason N. Johnson, MD, MHS, Ranjit R. Philip, MD, Ann Hyde, RN, and Benjamin S. Hendrickson, MD

Cardiovascular imaging demonstrated no evidence of myocardial injury or myocarditis in athletes following COVID-19 infection, according to a research letter published in *Circulation* by Le Bonheur Children's Hospital and University of Tennessee Health Science Center cardiologists. The screening and evaluation was conducted by Le Bonheur Heart Institute Sports Cardiology team members Benjamin S. Hendrickson, MD, Ranjit R. Philip, MD, and Ryan E. Stephens, NP-C, MBA, and Le Bonheur Director of Cardiac MRI Jason N. Johnson, MD, MHS. Researchers say this study confirms existing recommendations that cardiovascular screening can be deferred in COVID-19 positive athletes who are asymptomatic or have milder symptoms.

"Concern for cardiovascular disease as a result of COVID-19 brought about recommendations for evaluating athletes after infection," said Johnson. "Our results show that none of the athletes who underwent cardiac MRI had abnormal findings."

137 collegiate athletes from three universities were evaluated in Le Bonheur's sports cardiology clinic no sooner than 10 days after testing positive for COVID-19. The athletes, all young adults, compete across the National Collegiate Athletic Association (NCAA) Divisions 1, 2 and 3 and represent a broad range of sports and various racial ethnic backgrounds – 48% black, 47% white and 7% Hispanic.

Le Bonheur cardiologists used an algorithm-guided screening to evaluate the athletes. Regardless of symptoms or illness severity, cardiologists obtained a 12-lead electrocardiogram, transthoracic echocardiogram and conventional cardiac troponin I (cTn) level from each COVID-19 positive athlete. If any of these tests were abnormal or the athlete had a clinical evaluation of concern, they were referred for cardiac MRI (CMR). Athletes with normal evaluations and negative tests or negative CMR slowly reintroduced exercise into their routine and eventually returned to full participation in sports.

Study findings include:

- Most athletes (82%) were symptomatic and experienced mild (67%) or moderate (33%) symptoms. None of the athletes had severe COVID-19 illness.
- Only five (3.6%) athletes had abnormal testing that required CMR. Of these five, none had abnormal CMR results consistent with myocardial injury or myocarditis.
- None of the athletes experienced new symptoms or other health problems after resuming exercise and normal competition.

"On the basis of the outcomes and follow-up in our cohort, it is reasonable to defer cardiovascular screening in asymptomatic athletes or those with milder COVID-19," said Philip. "Cardiac screening, testing and imaging can be guided by the severity of symptoms and illness in an athlete."

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Le Bonheur Children's Hospital

Examining nonstented repair of distal hypospadias

Joseph M. Gleason, MD

Nonstented tubularized incised plate (TIP) is safe and effective for distal hypospadias repair, according to research published by Le Bonheur Pediatric Urologist Joseph M. Gleason, MD, and colleagues in *Pediatric Urology*. To compare the complications of nonstented versus stented TIP repair, Gleason conducted a retrospective study of 195 patients who underwent nonstented TIP repair of distal hypospadias.

In hypospadias, the opening of the urethra does not form at the tip of the penis. Instead, it forms near the end of the penis (distal hypospadias), along the shaft (midshaft hypospadias) or where the penis and scrotum meet (penoscrotal hypospadias).

TIP is widely accepted for hypospadias repair, but the use of a stent in TIP has remained controversial. Previous research indicates stents may be associated with some complications, such as bladder spasms, pain and longer hospital stays.

Gleason and colleagues used their experience with nonstented TIP repair of distal hypospadias to investigate the rates of immediate and delayed complications. They hypothesized the rates of complications with nonstented TIP repairs performed at Le Bonheur would be similar to those of stented TIP repairs reported in the literature.

5.6% of patients who underwent nonstented TIP repair presented with immediate postoperative complications, including split urine stream, painful or difficult urination, inability to completely empty the bladder and blood in the urine. Of the original 195 patients, 142 had follow-up appointments at an average of 10.5 months after surgery. Of these 142 patients, 8.5% presented with at least one delayed postoperative complication, including an opening between the urethra and perineum, a narrowed opening at the tip of the penis and separation of the edges of the surgical wound.

The rates of both immediate and delayed complications were low following nonstented TIP repair of distal hypospadias. The delayed complications of nonstented repairs were also comparable to those of stented repairs. These results support the safety and efficacy of the nonstented TIP technique for distal hypospadias repair. Patient anatomy often dictates whether a stent should be used, and more complex repairs may contribute more to the development of delayed complications than the use of a stent.

Assadi, A., Alzubaidi, A. N., Cline, J. K., Sharadin, C., Travis, A.J., Marley, K., Dewan, C., & Gleason, J. M. (2020). Nonstented Tubularized Incised Plate Distal Hypospadias Repair: A Single Center 5 Years' Experience. Urology, 146, 207–210. https://doi.org/10.1016/j.urology.2020.08.014

Whitaker named CDC program ambassador, receives grant

Toni Whitaker, MD

Toni Whitaker, MD, professor of Pediatrics at UTHSC and division chief of Developmental Pediatrics at Le Bonheur, has been named state ambassador for the Centers for Disease Control and Prevention (CDC) program "Learn the Signs. Act Early." This program focuses on improving early identification of children with developmental disabilities and autism, with the goal of providing support to these children and their families. As the program ambassador for Tenn., Whitaker has received a $94,000 grant to collaborate with early childhood programs across the state to promote developmental screening and monitoring.

Pierre, Gosain receive NIH funding for project on host-fungal interactions in Hirschsprung-associated enterocolitis

Joseph Pierre, PhD

Ankush Gosain, MD, PhD

Joseph Pierre, PhD, assistant professor of Neonatology and Microbiology, Immunology & Biochemistry at UTHSC, and Ankush Gosain, MD, PhD, associate professor of Surgery and Pediatrics at UTHSC, received an NIH R21 grant to model host-fungal interactions in Hirschsprung-associated enterocolitis (HAEC). HAEC is a life-threatening complication of Hirschsprung disease, which causes intestinal obstruction in newborns, even following corrective surgery. Although microbes such as intestinal bacteria have been linked to HAEC, the precise microbial triggers of this condition have not been defined. Backed by NIH funding, Pierre and Gosain will examine interactions between gut fungi and immune responses of the intestinal epithelium, which lines the small and large intestine of the gastrointestinal tract. This research may shed light on fungal and immune contributions to the development of HAEC, thus providing potential therapeutic targets for this devastating condition.

Pediatric Fellows Research Day

On May 26, 2021, Le Bonheur, the CFRI and the UTHSC Pediatric Fellowship Office hosted the inaugural Pediatric Fellows Research Day on Zoom. This virtual event was kicked off with a keynote speech delivered by Dennis Black, MD, professor of Pediatrics and Physiology at UTHSC, scientific director of CFRI, and vice-president for Research at Le Bonheur.

Eight pediatric fellows across multiple pediatric subspecialties, including cardiology, endocrinology, neonatal-perinatal medicine, nephrology, pulmonology and surgery, presented their fellowship research projects. The topics ranged from risk factors of acute kidney injury in children with COVID-19 to a new scoring system for Hirschsprung-associated enterocolitis. All talks are available online at https://tinyurl.com/aje6akjc.

Le Bonheur cardiologists conduct first successful long-term use trial of platelet inhibitor cangrelor in pediatric patients on VADs

Cangrelor, a novel, intravenous $P2Y_{12}$ platelet inhibitor, can safely be used as a long-term antiplatelet therapy for pediatric patients on continuous flow ventricular assist devices (VADs), according to research published in *Artificial Organs* by Le Bonheur cardiologists and led by former Le Bonheur Pediatric Cardiology Fellow Sarah E. Fahnhorst, DO. While previous studies have demonstrated viability of cangrelor in adult populations, this was the first study published on successful long-term use of cangrelor in pediatric patients.

Former Le Bonheur Pediatric Cardiology Fellow Sarah E. Fahnhorst, DO (at left)

"Thromboembolic events and bleeding are major sources of morbidity among pediatric patients supported on a VAD," said Fahnhorst. "Cangrelor is short-acting, reversible and intravenous, making it a feasible antiplatelet agent in select pediatric patients."

Pediatric patients who are unable to take or do not respond well to other antiplatelet drug options can safely remain on a VAD by using cangrelor. This allows for a lower risk of blood clotting or bleeding complications.

For optimal VAD function, pediatric VAD patients require a delicate balance between combatting blood clot formation and preventing bleeding episodes. This dilemma has prompted development of new strategies to mitigate risks. In addition, 20-40% of the population are poor metabolizers of common antiplatelet drugs and do not have an adequate response to these drugs. Therefore, an alternative option to long-term antiplatelet therapy is necessary for patients who need this crucial treatment.

The study followed seven patients at Le Bonheur who had end stage heart failure and were supported on continuous flow VADs. The majority of patients were started on cangrelor because of impaired enteral absorption of oral $P2Y_{12}$ antagonists or due to an inability to reach therapeutic goals. The median duration of a patient receiving intravenous cangrelor was 43 days.

Patients on cangrelor reached the therapeutic $P2Y_{12}$ level in a mean of 1.86 days. No cerebrovascular events occurred while on cangrelor. There were two episodes of mild gastrointestinal bleeding, one episode of hematuria and one pump thrombosis. The number of these events are comparable or reduced when compared with statistics from previous studies. Adequate platelet inhibition was achieved quickly and with a much lower dose of cangrelor than previously reported by the manufacturer.

This study showed that cangrelor is a successful, viable, long-term antiplatelet therapy in select pediatric VAD patients. Future studies would benefit from a larger sample size with a control group to further evaluate safety and effectiveness in the pediatric population.

"Cangrelor addresses some of the major pitfalls of oral antiplatelet therapy, including impaired enteral absorption, reversibility and epigenetic factors," said Fahnhorst. "As more pediatric patients are placed on VAD support, cangrelor may be a feasible antiplatelet strategy."

IN BRIEF

The new NIH biosketch

The National Institutes of Health (NIH) has issued a new biosketch format, which should be used for all NIH grant applications and Research Performance Progress Reports due on or after May 25, 2021. On Jan. 25, 2022, the NIH will require use of the new format and may reject or delay applications using the old format. All changes listed below pertain to the Non-Fellowship Biographical Sketch:

- In Section A "Personal Statement," mention ongoing and completed research projects from the past three years that you want to highlight. This information previously went in Section D "Research Support."
- The title of Section B has changed from "Positions and Honors" to "Positions, Scientific Appointments and Honors."
- Section D "Research Support" has been removed.

To easily update your biosketch, you can use SciENcv on the NCBI website. You can copy and paste your information into the relevant text fields on SciENcv, which will create a properly formatted biosketch that you can download as a PDF or Microsoft Word file. For assistance with your biosketch, please contact Courtney Bricker-Anthony, PhD, CFRI scientific editor, at courtney.bricker-anthony@lebonheur.org.

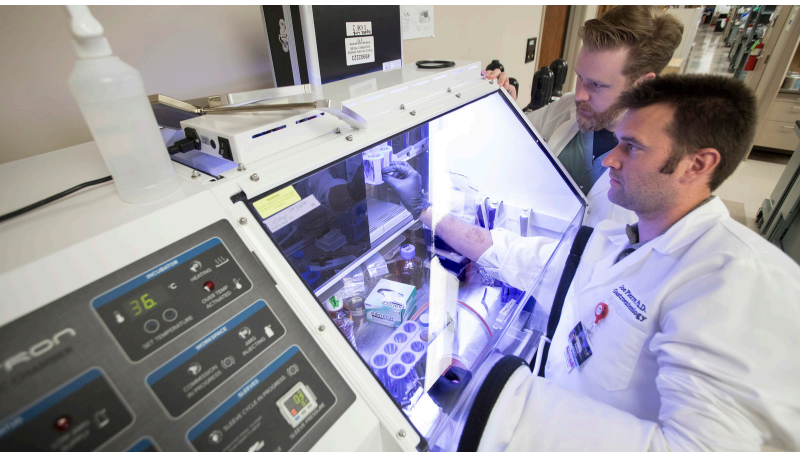
FDA issues notice of noncompliance with ClinicalTrials.gov requirements

Under current federal law, researchers are required to register clinical trials of drug products, biological products and device products on ClinicalTrials.gov within 21 days after the first human subject is enrolled. The summary results for these trials must also be submitted no later than one year after the study's completion date. The FDA recently issued the first Notice of Noncompliance for failure to submit summary results to ClinicalTrials.gov. The FDA has the ability to issue monetary fines and pursue criminal litigation for failure to comply.

If you are runing a clinical trial or plan to conduct a clinical trial, please ensure that you are in compliance with all federal laws regarding ClinicalTrials.gov, as the FDA is currently conducting an audit. Please also note that clinical trials cannot be published in peer-reviewed journals if they are not registered on ClinicalTrials.gov.

For assistance with clinical research and regulatory matters, please contact Kerry Moore, CFRI director of clinical research, at kerry.moore@lebonheur.org.

Linking metabolism with gut mycobiome



Joseph Pierre, PhD (far right)

Gut fungi may contribute to important aspects of health, such as metabolism and accumulation of body fat, says new research from investigators at UTHSC and Le Bonheur. In the study published in *Communications Biology*, Joseph Pierre, PhD, and colleagues explored potential links between the gut mycobiome (the fungal community of the microbiome), the environment and metabolism in mice exposed to a standardized or processed diet for eight weeks. Results showed that changes in the mycobiome could potentially contribute to increased fat mass and insulin resistance, which are hallmarks of obesity. These findings could have important implications for conditions such as obesity and diabetes.

The standardized diet had a normal balance of carbohydrates, fat, fiber and protein. To mimic an unhealthy western diet, the processed diet was high in carbohydrates and fat, contained normal levels of protein and lacked fiber.

On the standardized diet, gut fungal communities showed decreased diversity over time and became more homogenous. However, these fungal communities remained distinct from one another. On the processed diet, gut fungal communities also showed decreased diversity over time but converged and were no longer distinct. The composition of fungal communities was also markedly different between mice on the processed diet and mice on the standardized diet.

These changes in gut fungal community composition in response to the processed diet were linked to changes in body composition and metabolism. Most mice gained fat mass on the processed diet. This increased fat mass was associated with increased fasting leptin and ghrelin in addition to decreased resistin; leptin, ghrelin and resistin are hormones associated with hunger suppression, hunger stimulation and insulin resistance, respectively. Changes in the abundance of two types of fungi, *Thermomyces* and *Saccharomyces*, were associated with increased triglyceride concentrations in the blood and fat deposits in the liver.

This study shows that the makeup of the mycobiome is dynamic and responds to environmental and dietary changes. These findings could have important long-term implications for conditions such as obesity and diabetes.

Mims TS, Abdallah QA, Stewart JD, Watts SP, White CT, Rousselle TV, Gosain A, Bajwa A, Han JC, Willis KA, Pierre JF. The gut mycobiome of healthy mice is shaped by the environment and correlates with metabolic outcomes in response to diet. Commun Biol. 2021 Mar 5;4(1):281. doi: 10.1038/s42003-021-01820-z. PMID: 33674757; PMCID: PMC7935979.

Racial health disparities in Type 1 diabetes and COVID-19 infection

Non-Hispanic black patients with Type 1 diabetes and COVID-19 were almost four times as likely to present to the hospital with diabetic ketoacidosis (DKA) compared to non-Hispanic whites, according to an article published in *The Journal of Clinical Endocrinology & Metabolism* by Le Bonheur Pediatric Endocrinologist Kathryn Sumpter, MD.

The study examined 180 patients with Type 1 diabetes and laboratory-confirmed COVID-19 from 52 clinical sites, including Le Bonheur. The objective of the study was to evaluate instances of DKA, a serious complication of Type 1 diabetes, and COVID-19 and to determine whether minorities saw increased risk when controlled for sex, age, insurance and last hemoglobin A1c (HbA1c) level.

"We know that Type 2 diabetes is a risk factor for worse COVID-19 outcomes, but less is known about Type 1 diabetes and COVID," said Sumpter. "This study allowed us to examine the intersection of Type 1 diabetes and COVID while also determining the racial inequities in DKA for these patients."

The results of the study show that non-Hispanic black patients with COVID-19 and Type 1 diabetes have additional risk of DKA beyond the risks associated with diabetes or minotirty status. Non-Hispanic blacks were more likely to present with DKA and COVID-19 (55%) compared with non-Hispanic whites (13%).

Kathryn Sumpter, MD (right)

"A combination of factors related to social and structural risks leads to higher rates of DKA among minority Type 1 diabetes patients with COVID-19," said Sumpter. "Social determinants of health, including income level, education, racial discrimination and inadequate health care access, impact these populations with devastating complications."

According to the study, intervention in these areas is essential to prevent higher-risk outcomes that disproportionately affect minority populations.