Dr. Carolyn L.: Welcome to Circulation on the Run, your weekly podcast, summary, and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Center and Duke National University of Singapore. On our podcast today we are discussing the role of diastolic stress testing and the evaluation of heart failure with preserved dejection fraction, a really hot topic indeed, but first here's your summary of this week's issue.

The first study tackles the obesity paradox in cardiac surgery, where morbidity and mortality are lower in obese patients. This study sought to ask the question, "Is this due to reverse epidemiology, bias, or confounding?" To answer this question, Dr. Maris Kelko and colleagues from University Leicester in United Kingdom used two separate analysis. One, registry data from the National Adult Cardiac Surgery Registry and two, a systematic review in meta-analysis of studies. Of more than 400,000 patients in the cohort study and more than 550,000 patients in the systematic review, the authors found a U shape association between mortality and body mass index classes, where lower mortality was observed in overweight and obese class one and two patients, relative to normal weight patients, and mortality was increased in underweight individuals.

Now, the obesity paradox has been attributed to reverse epidemiology where the survival benefit associated with obesity is thought to actually reflect worse outcomes in the underweight patients who also had frailty, cachexia, or severe chronic disease. However, in the current study, counter to the reverse epidemiology hypothesis, the protective effects of obesity were less in patients with chronic renal, lung, or cardiac disease and greater in older patients as well as in those with complications of obesity, such as metabolic syndrome and atherosclerosis. Furthermore, adjustments for important confounders did not alter the results. The authors therefore concluded that obesity is associated with lower risks after cardiac surgery with consistent effects noted in multiple analysis even after attempting to address residual confounding and reverse causation.

The authors even went as far as to suggest that their findings do not support common practice where weight loss is recommended prior to surgery or where very obese patients are refused surgery in the morbidly obese. These provocative findings are discussed in an accompanying editorial by Doctor's Carnethon and Kahn from Northwestern University. While the editorialists agree that this well-designed study highlights an important knowledge gap, they pointed out that the obese class two patients had nearly five times greater risk for deep sternal wound infection and 25% higher likelihood of needing renal replacement therapy.

In such patients additional intervention in the perioperative period may still be indicated and include weight loss recommendations and postoperative surveillance for complications. Thus, a more cautious final recommendation may be for future studies to prospectively assess weight loss interventions prior

to elective surgery in the context of overall surgical risk as assessed by the EuroSCORE or STS models.

The next paper describes mechanistic studies showing for the first time that nucleoside diphosphate kinase suppresses cyclic-AMP formation in human heart failure. In this paper by First Authors, Dr. Abu Taha and Hagemann, corresponding authors Dr.'s Tobref and Weilend from the Heidelberg University in Germany, the authors performed biochemical studies of nucleoside diphosphate kinase and G Protein signaling in human and rat tissue samples, assessed the functional impact of nucleoside diphosphate kinase C on cyclic-AMP levels and contractility and isolated red cardiomyocytes and determined that in vitro effects of these nucleoside diphosphate kinases on contractility in zebra, fish and mice.

They identified nucleoside diphosphate kinase as the critical isoform for the regulation of G Protein function and cyclic-AMP levels in the heart with important consequences for cardiac contractility. The increased nucleoside diphosphate kinase membrane content in human heart failure could potentially counteract a fading beta adrenoceptor response in the early stages of heart failure by increasing the amount of G Alpha stimulatory proteins in the plasma membrane. However, by switching from stimulatory to G Alpha inhibitory to activation, nucleoside diphosphate kinase may play a role in heart failure progression by reducing cyclic-AMP levels, typical for end-stage human heart failure.

The study, therefore contributes to a better understanding of the molecular processes, underlying alter G Protein signaling in heart failure, and may help to develop new heart failure therapies.

The next study tested the hypothesis, that high intensity interval training is superior to moderate continuous training in reversing cardiac remodeling and increasing aerobic capacity in patients with heart failure and reduced ejection fraction.

Doctor Ellingson and colleagues from the Norwegian University of Science and Technology, performed a multicenter trial, comparing twelve weeks of supervised interventions of high-intensity interval training at 90 to 95% maximal heart rate, moderate continuous training at 60 to 70% maximal heart rate, or a recommendation of regular exercise in 261 patients with heart failure and ejection fraction less than 35%, in New York Heart Association class II or III status.

The primary end point of change in left ventricular end-diastolic diameter from baseline to twelve weeks was not different between the high-intensity and moderate continuous groups. There was also no difference between the high-intensity and moderate groups in peak oxygen uptake, although both were superior to the recommendation for regular exercise. None of these changes

were maintained at follow up after 52 weeks. Serious adverse events were not statistically different. However, training records showed that 51% of patients exercised below the prescribed target, during supervised high-intensity interval training, and 80% above the recommended target in those with moderate continuous training. Given that high-intensity interval training was not superior to moderate continuous training, in reversing remodeling or improving secondary end points, and considering that adherence to the prescribed exercise intensity based on heart rate was difficult to achieve even in the supervised setting.

The authors concluded that moderate continuous training remains the standard exercise modality for patients with chronic heart failure.

The final paper tells us, that brain emboli after left ventricular endocardial ablation may be more common than we knew. First author Doctor Whitman, corresponding author Doctor Marcus and colleagues from University of California studied eighteen consecutive patients, scheduled for ventricular tachycardia or premature ventricular contraction ablation, over a nine month period. Twelve patients undergoing left ventricular ablation were compared to a control group of six patients, undergoing right ventricular ablation only. Heparin was administrated with a goal activated clotting time of 300 to 400 seconds for all left ventricular procedures. Pre impulse procedural brain magnetic resonance imaging was performed on each patient within a week of the ablation procedure. The authors found that seven of the twelve patients, or 58% undergoing left ventricular ablation, experienced a total of sixteen cerebral emboli, compared with none among patients undergoing right ventricular ablation. Seven of the eleven patients undergoing a retrograde approach to the left ventricle, developed at least one new brain lesion. Thus, more than half of patients undergoing routine left ventricular ablation procedures, experienced new brain emboli after the procedure, even in the absence of clinically apparent stroke.

Future research is critical to understanding the long-term consequences of these lesions and to determine optimal strategies to avoid them. This is further discussed in an editorial entitled "The Sound of Silence". How much noise should we make about post ablation silence strokes? By Doctor Z and Vora from Stanford University. Well, those were your summaries, now for our featured discussion.

I am so thrilled to have with me two special guests to discuss the topic of the diagnosis of heart failure preserved ejection fraction or HFpEF. As you all know, that's my favorite topic and I have favorite people with me today. First, the corresponding author of our feature paper, Doctor Barry Borlaug from Mayo Clinic, Rochester, Minnesota. And, for the first time on the podcast, Doctor Mark Drazner, Senior Associate Editor from UT Southwestern. So, welcome Barry and Mark.

Barry Borlaug: Thank you Carolyn.

Mark Drazner: Thank you, great to be here.

Dr. Carolyn L.: So, Barry, you talked about the role of stress diastolic testing, shall I call it, in the diagnosis of HFpEF in your paper. Could you tell us why you looked at it and what you found?

Barry Borlaug: Sure, Carolyn. When you have dyspnea and fatigue and you got a low EF, it's pretty easy to make the diagnosis of heart failure reduced EF, but we've been struggling for years with making the diagnosis of dyspnea, whether it's HFpEF or not in people with normal ejection fraction. And that's because physical and laboratory and clinical signs of high filling pressures and congestion, are either difficult to see or only present during stress, like physical exercise, in patients. So that's really what motivated us to pursue this study.

We took patients, that were referred to our cath lab for invasive hemodynamic exercise testing, so we directly measured filling pressures, PA pressures and cardiac output reserve, to get a gold standard assessment, whether people have heart failure or not. And then we performed simultaneous echocardiography and blood testing to measure NT-proBNP levels, and then we just looked at what we could figure out. Can you accurately discern HFpEF patients from patients without cardiac dyspnea, using these non invasive estimates.

We saw that a lot of people, with, for example, NT-proBNP levels that are low enough to be where most would consider HFpEF excluded, actually had HFpEF. And we saw that there were modest correlations between non-invasive echocardiographic estimates of filling pressures, specifically the E to E Prime ratio, and directly measured left heart filling pressures. But when we applied the criteria that had been initially proposed, we saw poor sensitivity to make the diagnosis with exercise. And this was largely related to the difficulty with getting all of the different echocardiographic indices, that are currently examined as part of the diastolic stress testing non-invasively. Next, we looked at just adding the exercise E to E Prime, which is an estimate of filling pressures, and when we used the cut-point, that's already been proposed, according to contemporary data, we found that this substantially improved the sensitivity to identify HFpEF, but there was a bit of a trade-off in that specificity decrease.

Dr. Carolyn L.: That's so cool. So let me summarize some of these take-home messages here. First of all, using just rest echo. I was really impressed to see that rest echo indices alone only identifies a third to maybe up to 60% of the patients you found with invasively proven HFpEF. So, we may be specific, but we're really missing quite a number of patients. And then if you exercise them, what your data is really showing is that it's better to exercise them and use this data for the negative predictive value, isn't that what you're saying?

Barry Borlaug: You know, the exercise is really the gold standard, so it gives you both, the negative and positive. With the echocardiography, relying on the exercise E to E Prime ratio, that was really helping us, as you say, Carolyn, with the higher negative predictive value. So most people, that had HFpEF, in this series, where we could get adequate, highly controlled environments, adequate diagnostic echocardiographic data, most people that ended up having HFpEF fit those criteria, we could see an elevation in this E to E Prime on exercise, so it did provide good negative predictive value.

Dr. Carolyn L.: These are just such important data, because I think we're all still struggling with how to make this diagnosis of HFpEF. Mark, could you just share some thoughts on whether you think this is going to really change practice, even change guidelines?

Mark Drazner: I think, if you read this paper, you would recognize it, that it's certainly a critical question that we're all facing, how to make the diagnosis of HFpEF. And all of their guidelines that have been advocated, there really wasn't much data, and these really are the best data out there. So, certainly, it's [inaudible 00:15:41] me a direction of changing practices. Barry says, certainly, the approach will need to be validated, I think, before it reaches high level guidelines, but certainly I think it's a step in the right direction, and points the way towards the future in terms of improving our ability to diagnose HFpEF. And really, that's why both reviewers and [inaudible 00:15:59] this is such an important paper.

Dr. Carolyn L.: Right. Barry, I have a quick question for you though. Doing exercise echo, not easy. E to E Primes are all over the place usually. How easy was it? How feasible was this test?

Barry Borlaug: So, first I'd like to say that we have outstanding, very well-trained, very highly skilled research scenographers, here at Mayo doing this. In very controlled environment, we're providing plenty of time for them to obtain images and that's going to be a question moving forward, because not everybody in clinical practice has that capability. But with that said, in this very controlled environments, skilled scenographers, we were able to measure the exercise data during low level exercise about 85 to 90% of the time and at peak exercise about 75 to 80% of the time. So, it's fairly feasible, but even in this best case scenario, we can't get it on everybody.

Mark Drazner: Even in the [inaudible 00:19:49] echo lab, the recommended approach by the ASE with the four measures. How many times they were not able to acquire all those images, are necessary for those four techniques and so, here you have a [inaudible 00:20:03] of AS echo lab not being able to do that, and being transparent about that, and [inaudible 00:20:08] to the community, saying that, although these are ideal measures, even the [inaudible 00:20:12] perhaps you can't acquire them. I think that was another important point that came out of this and then lead to the focus on the E to E Prime.

Barry Borlaug: I couldn't agree more. You got one of the world renowned labs, very skilled scenographers doing imaging, and we're still not able to get it all in each patient, and that just points to the difficulty of getting really high quality diagnostic images, and a lot of time you need the next level test, when that happens. And invasive exercise testing is really that test, the gold standard.

Mark Drazner: When you get echos from the outside and you look at the E to E Primes, are you confident that the data, that's generally acquired, is gonna be acceptable for this [inaudible 00:20:50]?

Barry Borlaug: Yes and no, I mean I'm always a little bit concerned, but it's not just being a control freak, you know, wanting to see everything, but I think that if it's a still frame doppler, tissue doppler spectrum, you can see that the sample volume is in the right place, and it's really unequivocally normal or abnormal, I feel pretty good about that. Not as good as when they get a full dedicated study here.

Mark Drazner: Of course, the gold standard is also difficult. The invasive measurement.

Barry Borlaug: Yes it is, I didn't [inaudible 00:21:18] that, but we've been doing a lot of invasive exercise tests for the last ten years now. And we do like 250 a year here, so we're really quite [inaudible 00:21:28] but we have all hands on deck in the lab. We have a couple technicians running gas samples around, all over the place. Somebody is on the medgraphics card, measuring oxygen consumption. We've got a nurse in there, that's helping out, so it's complicated, and of course we're using the micromanometer catheters for the pressure assessments, because you get so much more artifacts from width and under damping and over damping with the pressure tracing, so that's also not easy to do if you say.

Mark Drazner: So maybe for practicing cardiologists it's gonna be hard to duplicate that and perhaps spend the energy in terms of doing the exercise echo techniques off the speed, for example. Perhaps, it's another message.

Barry Borlaug: I would agree completely. And I think that again, when you do that, if you do a really high quality exercise echo and it's still not quite definitive, then you can refer on to a center that does have that capability, because obviously it's just reality, not everybody is going to be able to do this. Not every place has the size and resources to be able to do these really advanced tasks.

Dr. Carolyn L.: And do you apply exercise echo now in making your diagnosis? How do you use this data, for yourself, clinically?

Barry Borlaug: We started to think about this, and I think that the best case scenario where the people, that really have an intermediate pretest probability, based on their clinical characteristics. Somebody has jugular distension and a very high NT-proBNP level, and edema, you really don't need further testing, you know that

that's going to be HFpEF. And if somebody has no risk factors, and everything is stone cold normal, they don't.

But in some of these people that have some signals, but they don't quite meet criteria, we are doing this, again, if they have adequate echocardiographic images at rest. And then we're looking really carefully at the exercise echocardiography data, one concern from this data, I want to make sure people are very circumspect and really critically looking at the quality of their data, because we shouldn't over-interpret equivocal findings. And as you said earlier, E to E Primes can be all over the map, they're very difficult to obtain during exercise. But I think that if everything looks very high quality and is definitely abnormal or definitely normal, that can be helpful. More so, if it's normal. We did see more false positive, so if it is abnormal, we did suggest that you may want to perform further confirmatory testing, because of the higher false positive rate with exercise echo.

Mark Drazner:

I would say for the listeners, they should take a look at his figure six, which really is a nice diagnostic algorithm, where Barry shows, or advocates, for taking patients with intermediate probability and then using this to restratify that, using [inaudible 00:19:40] approach. I know that, that figure resonated with the editors and the reviewers dramatically, so I'd encourage listeners to take a look at that.

Dr. Carolyn L.: Listeners, you heard it right. [inaudible 00:22:36] Circulation on the Run. Don't forget to tell all your friends about this podcast and tune in next week.