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Key Words: mitral valve prolapse, mitral regurgitation, ventricular remodeling, primary mitral regurgitation, neochordoplasty, ejection fraction, heart murmur

Discussion

Presenter: Dr Daniella Corporan

Dr Amy Hackmann *(Dallas, Tex)*. Thank you, Dr Kane and Dr Ugalde, for inviting me and congratulations on this excellent work, Ms Corporan and Dr Padala. I have a few questions for you. I think the most burning for the audience is: How do we translate this work to clinical care? If we see a patient who maybe is graded only as moderate mitral regurgitation (MR) but has evidence of a dilated left ventricle (LV), should they be referred for early surgery, or we should we still continue to wait for just that severe MR threshold?

Dr Daniella Corporan *(Atlanta, Ga)*. Based on our studies, we see that there's early and progressive remodeling that occurs very soon after inducing MR. In our case, we see end-diastolic volume increased by 2 weeks, which is equivalent to 1 year in humans. If we look at the current guidelines, which are based off of ejection fraction, we see that the decline in ejection fraction occurs beyond the point at which there's already active and progressive remodeling. Our data

indicate that early surgery could be beneficial, but this needs to be confirmed in larger animals and patients as well.

Dr Hackmann. Thank you. What time frame do we have to intervene on patients? Is our window of opportunity for preventing long-term LV damage a few months, a few years, a decade? What should we recommend for patients?

Dr Corporan. That's a very interesting question. In our rodent model, we've characterized it out to 40 weeks, which is equivalent to about 20 human years. It depends on the indices that we look at. If we look at ejection fraction, it takes a very long time for that parameter to decrease.

But if we look at end-diastolic volume or the rate of change of end-diastolic volume, then those parameters change a lot sooner and so it looks like the 2-week time point, which is equivalent to about 1 year, could be a possible time point to intervene.

Dr Hackmann. Great. So if we start to see LV changes, we should intervene within a year. And since our goal here is to identify relatively asymptomatic patients but who have mitral regurgitation and the potential for LV damage, is there any kind of a screening biomarker or any type of other signal that we can look for in patients other than identifying depressed LV function and severe MR?

Dr Corporan. For the asymptomatic patients, there's currently no specific biomarker that's used in the setting of primary MR. But from some of the transcriptomic studies that we've shown, we've identified some very distinct pathways that are activated at that 2-week time point. In future studies, we want to investigate whether these can be detected as potential biomarkers to be used. In addition to the biomarkers that could be of value, also longitudinal tracing of these patients, possibly with biomarkers, but also with imaging-based LV parameters could be of value as well.

Dr Hackmann. You also showed that there was a very big jump in the end-systolic volume between the 10 and 20 weeks, which would be I guess about a 5-year period in a human patient. Do you know what can account for that? And do we see the same thing if we do longitudinal studies of patients with MR?

Dr Corporan. For that later increase in end-systolic volume, if we think about the LV structurally and what accounts for end-diastolic volume to increase rapidly, we know that cardiomyocytes can elongate to account for some increase in end-diastolic volume. But once that occurs, then that is when possibly the end-systolic volume and the contractile properties of the cardiomyocytes could be altered, which may explain why that occurs a little bit later. With longitudinal tracing, in the future it could be interesting to do some more experiments, potentially on the isolated cardiomyocytes themselves, to look at when exactly the function decreases.