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Extracellular Vesicle Therapy Improves Diastolic Performance and Reduces Perivascular Fibrosis in a High Fat Fed Porcine Model of Chronic Myocardial Ischemia

Presenter: Dr. Ahmed Mohamed Aboulgheit

Invited Discussant: Dr. Pavan Atluri

Dr. Philippe Menasché (Paris, France):

First of all, congratulations. I think it's a very important and interesting study, particularly because it's done in a large animal model. I have two questions for you. Number one, in one of your slides, it was indicated that you inject 50 micrograms of EVs. As you know, the international society rather recommends other metrics—for example the number of vesicles or the protein-to-vesicle number ratio.

My first question is, at least do you have an exact number of vesicles which were injected? And my second question is, because this study has to do with fibrosis, do you have some histological data regarding the infiltration of the myocardium by inflammatory cells—in particular macrophages, and of the phenotypic pattern of these macrophages?

Dr. Ahmed Mohamed Aboulgheit (Providence, RI):

Those are excellent questions. To address the first question, it's been our practice here to purify these extracellular vesicles, and we obtain a weight. Obviously the 50 micrograms of purified extracellular vesicles as our technique. Previously, we've shown results with this in terms of angiogenic properties and increased new vessel formation in the myocardium. But it is very interesting to quantify it in terms of a numerical or a count of vesicles, or ratio to protein as you said. So, this is something that we'll potentially be considering in the future.

Now, the second question is—we were initially interested in, as you mentioned, macrophages. But we went on to actually quantify myofibroblasts and the ratio of ASMA to vimentin, which we report in our paper that we've submitted recently to JTCVS. As a more sensitive sort of marker of myocardial infiltration with fibrogenic cells. And we report that this in fact was reduced with EV treatment.

Dr. Pavan Atluri (Philadelphia, PA):

Dr. Aboulgheit, I commend you, your mentors, and colleagues on yet another very nicely conducted hypothesis-driven translational research project. I thank you for sending me your paper early and enjoyed reading it. The body of work that your group has produced pertaining to the impact of MSC EV therapy in relation to comorbidities, namely hypercholesterolemia in diabetes, of course has been very impactful. In this study you have evaluated a very little thought-of yet very important aspect of cardiovascular disease, notably diastolic dysfunction.

The findings are interesting and thought-provoking. I do have a few questions to maximize our understanding of the therapeutic benefit that you present.

Why did you choose human MSCs rather than porcine? Do you have any concerns for immunologic tolerance? There has been quite a bit of dichotomy with our group amongst others demonstrating immunologic tolerance, yet others raising concerns about the potential for this tolerance. So why did you use human cells instead of porcine cells?

Dr. Aboulgheit:

For that very purpose of tolerance. That immunological reaction that may occur—we wanted to reproduce what would happen in the human model as closely as possible without any scrutiny in terms of using porcine cells. And with respect to tolerance, I personally don't know of any issues that have happened with tolerance among species but that would be interesting to look at.

Dr. Atluri:

I think it largely depends on what receptors we think are on the EVs that you isolate. Food for thought.

Do you have any control data on myocyte size for normal myocardium for age and size, matched sham hearts from your own samples? We traditionally have thought throughout this field, especially when we look for improvements in systolic function, the myocyte size is beneficial in terms of maintaining systolic function. So, it would be important to understand the baseline depreciate of preservation to normal. Do you have a comparator?

Dr. Aboulgheit:

We do have a sham model with the high-fat diet alone. And this in fact was reported in previous studies that the high-fat diet alone actually produces an increase or a higher performance in systolic function. We attributed this to many things like metabolic stress-induced pathways that promotes cellular proliferation as a result of metabolic stress. But yes, it'd be very interesting to compare that data with what we have at hand.

Dr. Atluri:

Your pressure volume data is very encouraging in terms of diastolic relaxation. Have you seen other measures utilizing your pressure volume analytics in terms of looking at improved cardiac flow? i.e. with improved diastolic relaxation —have you seen an improvement in cardiac output, stroke volume, or even end-systolic pressure-volume relationships?

Dr. Aboulgheit:

Yes, sir, we have. And we reported this in our previous paper, which was recently published in JAHA. We saw an increase in end-systolic pressure-volume relationship. We saw increased cardiac output. And we saw measures of increased non-volume-dependent measures of systolic performance with EV treatment.

Dr. Atluri:

Great. Congratulations on the nice body of work.