Discussion to: Intramyocardial injection of hypoxia-conditioned extracellular vesicles modulates apoptotic signaling in chronically ischemic myocardium

Presenter: Dwight Harris, MD
Invited Discussant: Rosemary Kelly, MD
Corresponding Author: Frank W. Sellke, MD

**Dr Dwight Harris (Providence, RI).**
Yes, the extracellular vesicles are obviously influencing many pathways. Whenever we’ve looked at our hypoxia-induced actually vesicles, we haven’t seen as many changes in, say, fibrosis as we’ve seen in some of our other pathways. But we have seen fibrosis changes with other types of extracellular vesicles. We’ve also looked at angiogenic signaling. There is some increase in angiogenic signaling, so that could be related to increased cardiac perfusion, increased cardiac function as well. We’ve looked at inflammation signaling. There seems to be a stronger decrease in inflammation with our hypoxia-induced extracellular vesicles than with our normal starved extracellular vesicles. So, it seems like the hypoxia-induced group is causing several different changes, and all of these together could be related to increased cardiac function.

**Dr Kelly.** And you mentioned that you see this as an alternative to revascularization. Is there a reason you wouldn’t want to consider in a patient population doing this alongside PCI or bypass surgery? Is there some reason you do one or the other, but not both together?

**Dr Harris.** I think that we’re looking at this as a novel technology. Obviously, that would be for the sickest patients to begin with, but certainly this could be combined with other therapies and other modalities. I think bypass surgery would be one of the easiest because what we’re doing right now is requiring an open injection. So, it could definitely be done concomitantly at bypass surgery in patients undergoing bypass surgery. The idea of stenting is a little more difficult. We’ve looked in our lab at different ways of delivering extracellular vesicles. We haven’t necessarily found as good a delivery using other methods as we have with the cardiac injection. So, you could perceive developing a stent that’s maybe coated with extracellular vesicles or something like that. But that would be a little bit further out than what we’ve studied, but maybe a potential also.

**Dr Kelly.** Okay. Thank you. And just finally, when you look at the work that you’ve been doing, can you just explain in this model why are you waiting until 5 weeks out before doing the injections? Is there a time frame that you are utilizing that in particular in this model?

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Dr Rosemary Kelly (Minneapolis, Minn). I’d like to thank Dr Harris for providing me with the manuscript in advance—it was very helpful—and to the society for allowing me to be a discussant. This is obviously work that is very important to me and near and dear to my research that I do. And it’s obviously coming from a lab that has spent years really investigating this work. So, thank you for sharing your most novel and updated work with us today. I also think it’s interesting that you’re addressing a question that was just brought up to Dr Mukherjee today in our plenary session. Can we really fix hearts rather than replace them with cell-based therapies?

So, I think we are maybe on the cusp of some really exciting work. I look forward to seeing other future work from you.

I do have a few questions. Beyond apoptosis, what other pathways of injury or recovery have you looked at with extracellular vesicles? And is there a mechanism that maybe there are alternative pathways that are going on beyond apoptosis?
**Dr Harris.** So, the injections are 2 weeks after the ameroid placement. The harvest is 5 weeks after the injection. For the timing for the injection, we like to model patients that already have coronary artery disease. So, this is meant to be a therapeutic, not a preventative therapy. So, we want to do it at a later time after they’ve already experienced some ischemic insult. With the ameroid constrictors that we’re using, we’re expecting closure of around 60% within the first week and that kind of progresses over the next 2 to 4 weeks. So that 2 to 4 weeks—that 2-week time point is a pretty good time point when the animals are already starting to experience some amount of ischemia.

**Dr Kelly.** And then why are you waiting out to the longer time then for the recovery?

**Dr Harris.** And then for the 5 weeks of therapy, this model is based on what we’ve seen with our previous models. So, when we’ve done this with a high-fat model using hypoxia, I mean, using normal condition starved EVs, and we’ve done this with a normal diet model using normal condition starved EVs, we used 5 weeks based on prior mouse studies at that point. And we have since continued to model that with our progressing work.

**Dr Kelly.** Thank you. And congratulations on your work. [applause]