Cardiovascular Risk Factors Associated with Smaller Brain Volumes in Regions Identified as Early Predictors of Cognitive Decline

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David F. Kallmes, MD Hello and welcome to this month’s video podcast in Radiology. I’m David Kallmes Deputy Editor for Neuroradiology. Today I’m joined by another Deputy Editor Albert de Roos who does Cardiovascular Imaging. We’re speaking today with Kevin King regarding his recent paper entitled “Cardiovascular Risk Factors Associated with Smaller Brain Volumes in Regions Identified as Early Predictors of Cognitive Decline.” Dr. King is Assistant Professor of Radiology at University of Southern California. Kevin thank you for joining us today.

Kevin S. King, MD Thanks for having me.

DFK So to get started, this study was focused on data from the Dallas Heart Cohort Study. I think it would be useful for our readers and viewers to understand a little bit about that study, the aims of it, and what the current status is.

KSK Okay sure. The Dallas Heart Study, it’s a large population based study that as the name implies was meant to look at cardiovascular disease. The size of the cohort originally started at looking about 6,000 people that got 3,000 of the people imaged with just cardiovascular imaging, maybe almost two decades ago now, and the main part of organizing a study like that isn’t just the numbers, but the way they sample people they try to do something similar to how a political poll might sample people so that whenever you study a group of 3,000 or 2,000 and you see a certain incident of disease, you can then take that larger and say that’s what the incidence of disease is in the entire county that we’re studying, so in a large major metropolitan center. So it’s more than just getting a lot of power; it’s also getting very accurate data of how significant different insults are in the population at large. So it’s not enriched at all for people with vascular disease. It’s really trying to make a sample as much as possible like the larger sort of population that you’re studying. Originally it was started to try to address disparities where there was very little African American involvement in some of the larger original heart studies. So it had a sort of disparities focus from the beginning. So it’s had over-sampling for African Americans. Beyond being sort of ethically important to do that I think there’s also a lot good scientific reasons for doing that. I work now with the Alzheimer’s Disease Research Center at USC and now that we’re starting to learn that vascular risk factors probably play a bigger part in causing dementia than we thought before, there’s a problem that a lot of these Alzheimer’s disease centers have really more well educated, higher socio-economic status people that are participating, so the level of vascular disease in the Dallas heart is a lot higher than what you would see in these cohorts. You have people that have more hypertension and more diabetes and also people that have less access to care. There’s a problem of if you look at the different populations, I think you can underestimate the impact of vascular disease if you’re looking in a convenience cohort from a major academic center versus if you invest and it really is a lot of time and effort to try to go out into the community and bring people in that maybe aren’t reading university newsletters or going by major medical centers and trying to bring them into the study. I don’t mean that to criticize the major neurology studies and Cliff Jack whenever he spoke to our group before had mentioned the wide disparities in funding, so there have been a lot more money going to heart studies in the past than have been going to neurology studies, so I think that they’ve had to try to make do with how much funding they’ve had, but going forward I think it would be really important to start, and people are doing this, start getting a lot of good data about brain health from some of the major heart studies.

DFK It’s interesting that Alzheimers studies are funded out of National Institute of Aging and not Neurology Diseases and Stroke Institute. In any event, so tell us for this current paper what was your research question and what did you find?

KSK The main question was to look at three areas that have gotten a lot of interest as far as early predictors, early predictors of Alzheimers disease although I just left it as early predictors of later cognitive decline in my description for the paper, and try to see for these three key areas that people have a lot of attention to, if we can see changes much earlier on related to vascular disease. The point there would be to see if they were having a big impact vascular disease risk factors on these areas that in the studies that had been published there may have been a component of vascular disease impacting the differenc-
es in brain volumes they've been looking at. As far as the specific hypothesis, I think I didn't know which brain regions the different risk factor would more correlate with, but this is sort of a beginning work and something where I'd like to see if you can establish specificity for how different risk factors involve different parts of the brain. So I guess the question would be would we see a different impact on like precuneus posterior cingulate hippocampus. The sort of counter theory to that is that certain brain regions are just going to be more susceptible to all types of insults, so there may not really be a characteristic pattern of involvement. A cure I really wanted to try to see if we could differentiate different parts of the brain, starting very simple, is three areas and see if we couldn't find a different profile of involvement for the three different brain areas.

**DFK** What data do you have to work from?

**KSK** We have longitudinal cardiovascular risk factor data. So the cohort that we have is really well characterized as far as heart disease, glucose tolerance. The outputs we had for the Dallas Heart and the limitation we had was it was a heart study. So we had less than ten minutes that we had available for brain imaging. They'd bring people in, they'd do an hour’s worth of scanning of the liver, of the aorta, the carotids, and so the brain was pretty minimal. So this study here was based off of just the volumetric T1 data and we haven’t had a huge imaging analysis component so likewise if you’re doing something like this now like the next step might be to use a sophisticated algorithm to really recognize the pattern of involvement of different brain regions. We’re working from a FreeSurfer analysis which I thought was still important the benefit of just doing region of interest. FreeSurfer analysis is it’s easy to understand. If you get more complex algorithms that show patterns of involvement, it can a little bit hard to relate to people and discuss what the findings are. There are still benefits to this simple approach, but starting with I just picked three areas with a particular interest to sort of the opening salvo into this question.

**DFK** So what did you find?

**KSK** The things that were interesting, one was finding relations with differences in volumes, so this is cross-sectional so forgive me if I sort of lapse into what I'm trying to get at which is atrophy, but for this we're just looking at cross-sectional differences. For people below age 50 we saw a number of factors that were associated with differences in volume for the posterior cingulate and precuneus. Alcohol being one that came up a lot and diabetes also came up. The thing that was kind of interesting for me that I wasn’t anticipating and maybe it was just my frame of mind, was that HDL actually ended up being associated with larger volumes which I wasn’t really anticipating thinking about things that might have sort of a protective effect, but this data would suggest that the HDL at least for some brain regions associated with higher brain volumes maybe it may be important with maintaining brain health and you have to be careful extrapolating the differences in volume here with outcomes. Some things may change volumes and they may not be responsible for the cognitive decline you see later on, so different things may produce the same sort of changes in the brain but have different meaning at least when we’re just looking at volumes, but that was sort of an unexpected thing for me. One thing that came out of that is talking with a group at Dallas Heart that has a lot more experience breaking apart the various parts of the lipidome and so subsequent work will try to tease that out a little bit better, because it wasn’t just HDL, some of the other triglycerides were also associated with high brain volumes. So I think there’s a lot to try to figure out there still.

**DFK** So Albert I know you have a strong interest in cardiovascular risk factors in the heart and the brain, is there anything you’d like to touch on in terms of mechanistic hypotheses that could be tested in a study like this?

**ADR** I was intrigued by the possible mechanism underlying this interaction between the heart and the brain. So there’s nowadays much interest in treating hypertension. Hypertension may affect the stiffening of the aorta and there’s also a lot of interest that heart disease and aortic stiffening may be part of the spectrum of Alzheimers disease and that it may be to a large extent a vascular disease. So how you envision how these cardiovascular risk factors work on the biomarkers which we can image with MR like heart failure, aortic stiffening, and how that interacts with the brain. Can you speculate a little bit on this possible link?

**KSK** Sure. So the sort of most direct way that you think they might be working is causing arterial sclerosis just leading to ischemic changes to the brain. So we have a sub-study that we just finished imaging of 70 people for the Dallas Heart where we’re going to be looking at stroma vascular reactivity. So we have a test where we can try to look at small vessel function. The idea there is is that the assumption is that this is mediating a lot of these vascular disease impacts on the brain. There are different options and there may be a direct neuronal effect. I’m looking at microvascular ischemic disease. There is also a very big push by (inaudible) and others to say that it is microvascular disease but it’s not ischemia. I think as radiologists usually think of it, but it may actually be differences in blood brain barrier permeability letting things that are harmful in the blood into sort of the extra cellular (inaudible) space around neurons. And so I came to USC now to work with (inaudible) and Krishna Nayak who have sort of made advances in DCE, just different ways of looking at gadolinium going in and out of membranes to try to better quantify blood brain barrier disruption. So that the short of it is I think going forward I think radiology is getting much better tools, not just looking at correlation with biomarkers, I think we’re getting much better about really being able to interrogate these
specific theories of how things are impacting the brain. I think the first thing is just to see which risk factors are important which is what this paper was, and to see do they even have anything to do with brain changes, and if so the other big thing is when. Are these things that are happening well before onset of neurodegeneration? Are they having their own separate processes of change in the brain? So much we’re looking at just before, right before people become demented because you don’t want to study people for 50 years, but it’s important to see maybe a lot of these processes stared earlier on and sort of related to this work, but something that was done really nicely, Cliff Jack at Mayo had some really nice work looking at how the hippocampus changes across adult lifespan. I think that there’s some big people in the field that are really starting to move in this direction to try to take a bigger approach as to how vascular risk factors across the life span are changing brain volumes.

ADR So I have also a question about possibilities for treatment of those patients because when you have these vascular emodynamic alterations you may affect them with treatment options. Some people have a somewhat positive attitude for clinical practice in this respect. Do you envision some practical and positive applications of these techniques for treatment options?

KSK I think one of my best qualities as a researcher is I have almost unbounding blind optimism that things I’m doing will have some impact. Let me try to relate why I think these things are important. As you and I were discussing a little bit before the broadcast began, one example of how treatment might be impacted is this current debate about what is the optimal blood pressure for maintaining health particularly as people become older. And so you had two different studies that have come out, well one the SPRINT Study that’s looking at data and another one that is looking into meta-analysis for prior health data that have reached different conclusions for where target blood pressure should be. The point that is important for this conversation is that the outcomes for that study is looking at really large vessel ischemic disease, you’re looking at cardiovascular disease, you’re looking at heart attacks and strokes. Those studies haven’t really been informed yet for what’s the best blood pressure to stop microvascular ischemic disease in the brain and to prevent dementia. That’s not really a part of those recommendations. And so the way it will go right now like it has for prior studies like the Honolulu Aging Study and others that show that hypertension in mid-life leads to dementia. Without better imaging markers, we’re just going to end up having to wait a couple of decades and seeing okay which blood pressures were related with more dementia and which were with less. A more sophisticated approach would be to look directly at vascular function which is what I’m focused on now to try to get a better test of exactly what is directly the microvascular function at this point in time so whenever you change blood pressure you can try to assess more quickly how is that impacting the brain as opposed to waiting for the ischemic changes to become so great that you have changes in the tissue. But I still have a lot of respect and I think there’s a lot of potential for getting much more out of just our basic volumetric T1s and my interest there really stems from wanting to have things be clinically useful so the metrics that we’re looking at in this study are something that pretty much any center that does MRI could get these metrics. The main problem has been really having these companies get FDA approval, so like NeuroQuant has something out there where if you wanted to get brain volumes you could look at them, but they don’t have the full suite of the underlying volumes that could be available from its FreeSurfer algorithm. So I think there’s going to have to be a little of a change in how we practice radiology in the future. It’s going to also be hand-in-hand with neurology and understanding what these brain regions mean, but we need to get a better idea of how risk factors like hypertension are impacting the brain, where they’re impacting the brain, and then I think that will help then to guide future treatments. I haven’t spoken about what specific treatments I think might be best, and so maybe I’ll throw out one quick counter thing that people would say that we know treating hypertension is useful so why do you need to study it, you just need to control it. But like this other discussion we’re talking about maybe we don’t know the ideal blood pressure that people need to really have it set at, or just to look at the experience that cardiologists and renal doctors have had where there may be therapies that are good for certain individuals in certain cases and not as good for others. A lot of these drugs we really don’t know how they’re changing transmission of pulsatility to the brain. We don’t know what impact they’re having on the vasculature within the brain itself. So I think there’s a real potential to come up with drugs that are more neuro-protective in the future and formed by this better understanding of the physiology.

ADR Okay thank you for the interesting discussion. I will refer to David Kallmes for concluding this discussion. Thank you.

DFK Yes, thanks to both of you. It’s been really stimulating and like a lot of papers your paper seems to raise many questions as it answers, which is good. A hypotheses generating paper is always a nice one to have in our journal. We’re very excited about your paper. Congratulations and we hope that your future studies you talked about today will also be sent to our journal for consideration. Thank you.

KSK Thank you very much.