Is Hepatic Triglyceride Content Associated with Aortic Pulse Wave Velocity and Carotid Intima-Media Thickness? The Netherlands Epidemiology of Obesity Study

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Ralph L. Widya, MD • Renée de Mutsert, PhD • Jos J. M. Westenberg, PhD • Karin B. Gast, MD, PhD • Martin den Heijer, MD, PhD • Saskia le Cessie, PhD • Johannes W. A. Smit, MD, PhD • J. Wouter Jukema, MD, PhD • Frits R. Rosendaal, MD, PhD • Albert de Roos, MD, PhD • Hildo J. Lamb, MD, PhD • For the NEO Study Group

Herb Kressel Hi. This is Herb Kressel, Editor of Radiology and welcome to the October 2017 Radiology podcast. Today, I’m delighted to be joined by Professor Hildo Lamb who is Professor of Radiology at the Leiden University in Holland, and who with his colleagues, actually in Leiden and throughout the Netherlands, wrote a very stimulating paper entitled, “Is Hepatic Triglyceride Content Associated with Aortic Pulse Wave Velocity and Carotid Intima-Media Thickness? The Netherlands Epidemiology of Obesity Study.” Welcome, Dr. Lamb. Thanks for joining us again.

Dr. Lamb Yeah, thank you for another opportunity.

Dr. Kessel It’s a pleasure. So, first thing’s first. What exactly is The Netherlands Epidemiology of Obesity Study?

Dr. Lamb It’s a large cohort study that we initiated in 2008, so now almost ten years ago and we included more than 6,000, it’s almost 7,000 patients in total and about one-third of those patients also had imaging and in that imaging part, we had different randomizations. One of the randomizations was to image the aorta and the cardiovascular part, but also some of them were included in the arm to measure the carotid IMT, the intima-media thickness and lots of other things like blood work, neurologic testing, and all kinds of things that were not included in this paper, but for this particular topic we ended up with almost 2,000 patients for the statistical analysis.

Dr. Kessel Right. So can you just share with us the specific study rationale? Why did you target this particular content? Why would one expect that hepatic triglyceride content should independently be associated with pulse wave velocity and/or carotid artery intimal wall thickness?

Dr. Lamb At first this seems a really strange association that you might think, “Well, what has the liver to do with the cardiovascular system?” It was actually based on experiments some time ago based on dietary interventions where we observed sort of co-variants in lipid levels in the liver and normal cardiovascular function and vessel stiffness and then we developed this concept in the end that we think that all over in the body the process is more or less the same, like in atherosclerosis. So first, you may have fat accumulation, then in response you develop inflammatory processes and based on that you have collagen formation and scarring. So what we thought maybe that the liver is the central organ in this process and that the liver actually directs all these changes all over in the body. So the idea was to study the link between fatty liver and other organs and in this case we were interested in two separate processes - the vessel stiffness and as a separate process atherosclerosis by measuring the intima-media thickness by ultrasound.

Dr. Kessel So blame it all on the liver.

Dr. Lamb Yeah, maybe that’s a good thing to remember.

Dr. Kessel The liver is the root of all of joy and problems. Okay. Very interesting. So another thing that some of those listening and viewing the podcast may be curious about, can you tell us a little more about pulse wave velocity alterations in the aorta and what’s the presumed mechanism of this in relation to atherosclerosis and to brain changes as well?

Dr. Lamb In general, it’s a complicated process. The name is also difficult, pulse wave velocity, but what it actually means is that we tried to measure the propagation of the ampules by the heart ejection. So we do not measure the flow or the flow volume. It’s just measuring how the blood propagates through the aorta and you can compare this for example by water flowing through a pipe. If the pipe is very stiff, the transportation time of the water from the pump to the distal end of the tap is very fast, so the speed of the fluid is decreased a little bit. So high pulse wave velocity reflects a stiff pipe and in this case stiff aorta, and the idea is that this is maybe related to atherosclerosis, but we are not sure if this is really the cause or effect. We think that this is related to the balance between the elastin in the vessel wall and the collagen level and we also know that this ratio is different between the
central part of the arteries and the peripheral arteries. For example, there is a difference between the central aorta and the peripheral vessels like the carotid artery where we measured intima-media thickness.

**Dr. Kessel** I see. Very good. Now, a little more about your study design. What did you actually do to study your hypothesis and study the associations? How did you choose the cohort? Did you have any subjects with elevated triglycerides who were not obese, as this is primarily the obesity study. So how did you go about answering the question you asked?

**Dr. Lamb** Well, the only major inclusion criteria was to be healthy or that you don't have a real known cardiovascular disease or diabetic disease, but actually it was a quite open study. So also we included normal people with normal BMI and also we had people in the overweight category between a BMI of 25 and 30, and obesity group with a BMI higher than 30. And based on the results of blood measurements in the patients, the blood work, we afterwards corrected the findings. So for example, we also included the lipid work, the lipid levels, use of lipid lowering medication, and we used all this data to detect confounding factors in our statistical model. So actually everybody was welcome in the study and afterwards we were using the statistical tricks and that is possible because it's a relatively large cohort.

**Dr. Kessel** Yes. So if you can tell us, briefly summarize your key findings.

**Dr. Lamb** The key finding is best shown in Figure 2. That is the easiest way to understand. So actually what we found is that if you have higher triglyceride content in the liver, so you have a fatty liver, that also the vessel stiffness or the pulse wave velocity is higher. Also on the other end of the spectrum, we slowed that with a lower BMI and with low liver fat, that also your pulse wave velocity is lower. So this confirms the feeling we had from previous studies and small studies that in this large cohort we indeed have an association or some sort of statistical link at least between the fat level in the liver and vessel stiffness. On the other hand, we also found relation between the carotid intima-media thickness that was a little bit higher in the patients with higher liver fat. Then it's always difficult to interpret these statistical numbers, so for the intima-media thickness it means that in the real world if you have a ten-fold increase in your fat level in the liver, then a 15 micrometer increase in your intima-media thickness happens. So that's the way how you have to interpret these results. The same is true for the vessel stiffness, for the pulse wave velocity. So if this fat level in the liver increases ten-fold, then you have about a 0.2 increase in your meter per second speed of vessel stiffening. So that's how you can look at these numbers.

**Dr. Kessel** Good. So can you kind of review how you identified this as independent of the other features of the metabolic syndrome?

**Dr. Lamb** Yeah, that's always nice of those larger cohort studies that you can use all the information you have and run different models. So what we normally do is start with the crude model, that's usually model 1, also in this study. Then we chose to use model 2 to check the confounding effects of general things like age, sex, blood pressure, heart rate, but also alcohol use, smoking habits, use of antihypertensive drugs, lipid-lowering drugs. So that's model 2. And then on top of that, we were more specifically interested in the factors determining the metabolic syndrome. That was model 3. And in model 4 it was everything and also on top of that of the visceral adipose tissue and the total body fat. And actually in that model 4 all the factors we could imagine are included there that could confound the results and even in that situation, we had a significant correlation or association between the liver fat and the pulse wave velocity and the liver fat and the intima-media thickness of the carotid arteries.

**Dr. Kessel** So are these models basically regression analyses or is it-

**Dr. Lamb** No, mainly ANOVA linear analysis.

**Dr. Kessel** Very good. Now one thing I noticed is that you had a - at least it was termed - a high failure rate in the acquisition of MR spectroscopy, which you used as the metric for hepatic fat, and with approximately a third of the patients there wasn't usable data. What do you think this was due to? Not allocating sufficient time for the exam or some lack of training?

**Dr. Lamb** That's an interesting question. I think it's mainly due to the technical challenges you have to perform spectroscopy studies in general. In the liver it's one of the easiest variants of that. In the heart, for example, it's much more complicated. So we had a learning curve for the technicians. That was one factor. So in the beginning, they missed out a lot of scans because you have to perform it with and without water suppression and sometimes we had two spectra with water suppression, two spectra without water suppressions, so that was a problem in the beginning and it was also a reason why we started developing newer techniques, so now in new studies we prefer to use the imaging-based Dixon-like techniques where you have a very easy setup and everybody can do the scan.

**Dr. Kessel** I see. Well, that certainly makes sense. And you mentioned looking at the lipid-lowering drugs. What was the effect of these when you kind of analyzed it in the regression models?
Dr. Lamb  Yeah, for the parameters we studied, that actually then - the difference between model 1 and 2, there was an effect. The significance of the model went down of the beta actually of the association, but still it was statistically significant. So there was an effect, but it did not explain the relation fully between the fatty liver and the vessel stiffness and the IMT thickness.

Dr. Kessel  Okay. So they sort of moved down the curve of the response curve if you will.

Dr. Lamb  Yeah.

Dr. Kessel  Okay. And going forward, what do you think are the potential clinical and public health implications of your findings other than everyone should control their weight? Are there other implications?

Dr. Lamb  Yeah, there is one interesting pathophysiological finding that’s a little bit more detailed, but we found a difference between the IMT measurements association because there was an effect of visceral fat. Actually, when we included visceral fat in model 4, the relation between the liver fat and IMT thickness was not significant anymore, but in the vessel stiffness, it didn’t matter. So the significance even got better. So this may indicate that the pathophysiological process behind atherosclerosis is a little bit different, different pathway, different factors than the vessel stiffening itself. On the other hand, if you are very practical, we know from literature and we performed a couple of those studies before, that there is still hope because if you do a diet, then also the pulse wave velocity changes. So it is still reversible if you are in a sort of sweet spot area.

Dr. Kessel  Well, thank you very much. This is very exciting work and we look forward to seeing the results of your future manuscripts and thank you so much for joining us today.

Dr. Lamb  Okay. Thank you very much.

Dr. Kessel  You’re welcome. Bye bye.

Dr. Lamb  Bye bye.