

Stiff vessels approached in a flexible way

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Valorisation

Introductory remarks

ARTERIAL stiffening is a key aspect in the development of cardiovascular disease (Laurent et al. 2006). Cardiovascular disease was responsible for 27% of all deaths in the Netherlands in 2014 (Centraal Bureau voor de Statistiek 2016a), a percentage that is expected to rise in our ageing population (Centraal Bureau voor de Statistiek 2016b; Lakatta and Levy 2003a; Lakatta and Levy 2003b). Arterial stiffening makes the arteries less compliant. In a healthy individual, this compliance reduces the force required by the heart to eject its blood. In patients with reduced compliance, therefore, more force is required from the heart, potentially leading to heart failure. Therefore, accelerated stiffening is a strong predictor of cardiovascular complications (Ben-Shlomo et al. 2014; Laurent et al. 2001; Van Bortel et al. 2012).

In this chapter, we will address the valorisation potential of the arterial stiffness research as performed in this thesis. This chapter is structured according to two aspects of valorisation (Drooge et al. 2013): 1) making knowledge available and suitable for economic and social exploitation; and 2) translating this knowledge into products, services, processes and new business.

Making knowledge available and suitable for economic and societal exploration

Part of the work presented in this thesis is directly and clinically applicable. Chapter 2 on pressure dependence of pulse wave velocity (PWV) gives clinicians a direct handle to more realistically interpret arterial stiffness measurements. Instead of assuming PWV to be an independent marker for arterial stiffness, it can now be interpreted in the context of the actual blood pressure. This is relevant, as this directly influences the intensity of antihypertensive treatment. Economically, this potentially leads to less use of antihypertensive medications.

A first step in making knowledge available is sharing it among peers. In this context, the results from this thesis have been presented at numerous conferences, generating much interest by other researchers. In addition, the majority of the chapters are published in scientific journals, or are submitted for publication therein. As this thesis was written from a *medical* engineering perspective, we aimed to publish our work not only in engineering journals (e.g., chapter 11 in *Biomechanics and Modeling in Mechanobiology*), but also in medical journals (e.g., chapter 2 in *Journal of Hypertension*) in order to directly address both clinicians, but also researchers as our target groups. As the implications of the work presented may directly influence patient treatment, patients are also among the target

groups. Patients will benefit from this work through their clinicians' better understanding. These clinicians can now more specifically prescribe anti-hypertensive treatment.

Whereas we strongly feel that knowledge availability is important for *all* research findings, whether positive or negative, we would like to highlight two products of knowledge that emerge from this thesis. First, the research on the pressure dependence of pulse wave velocity that was presented in chapter 2 was performed with the aim of clinical applicability in mind. Instead of using very detailed models of arterial mechanics (like in chapter 8), we used a very simple, exponential model approach to assess pressure dependence. This has the advantage that our method can be readily applied to clinically available measurements. Indeed, our method has already been applied to data from two separate patient cohorts (chapters 2 and 3). When we presented these studies at clinical conferences, it was very well received. As an example, I gave an invited talk summarising our work on pressure dependence of arterial stiffness at the European Society for Hypertension 2016 meeting in Paris (see About The Author). Discussion after this talk has led to two new collaborations, in which our pressure correction approach is also going to be used. Second, in the General Discussion of this thesis, we formulated an updated set of recommendations for the assessment of arterial stiffness. These recommendations could be directly translated to clinical practice and thereby affect clinicians, but also patients.

Until now, pulse wave velocity was generally corrected for blood pressure by means of a statistical approach. However, in this thesis, we present an innovative approach that is applicable to individuals (chapter 2). We furthermore critically assessed a commercially available method (cardio-ankle vascular index, CAVI), that is presented as blood pressure-independent. During this assessment, we found, in the context of CAVI's intrinsic assumption of an exponential pressure-diameter relationship, that this method yields slightly pressure-*dependent* values of arterial stiffness. This finding is important for CAVI users, so that they are aware of possible blood pressure-induced changes in this measure.

The knowledge availability that this section pertains to will be planned and realised by disseminating and communicating our results in various ways. We will ensure that all knowledge becomes available through academic publication. Furthermore, we actively communicate our findings at scientific, medical conferences to ensure that we also reach our clinical target audience. Through our active membership of the European Society for Hypertension Working Group on Vascular Structure and Function, as well as of the European ARTERY society, we will ensure that our findings are taken into consideration when new guidelines for the treatment of hypertension are formulated.

Translating knowledge into products, services, processes, and new businesses

Chapters 8 to 12 are all targeted at the *interpretation* or *understanding* of changes in arterial stiffness. This aspect of arterial stiffness is relevant, as it may provide new insights into the causes of arterial stiffening, and thereby may also elucidate potential targets for anti-stiffness medication.

Target groups for translation include pharmaceutical companies, medical device companies, other groups performing pre-clinical research and companies producing labora-

tory equipment. In chapter 8, we presented a method to interpret *in vivo* arterial stiffness measurements in terms of the individual wall components: collagen, elastin, and smooth muscle cells. By this means, a pharmaceutical company can e.g., monitor non-invasively what effect anti-hypertensive/anti-stiffening medication has on the wall components. The aforementioned modelling framework could also be implemented in e.g., the software of an ultrasound scanner. This would equip such a scanner with the direct capability to disentangle arterial stiffness effects on-the-fly, directly in the clinic. Furthermore, in chapter 12, we presented a set-up for pulsatile characterisation of murine arteries. Such set-up may provide relevant novel insight to researchers at various groups who are currently studying murine arteries. In many cases, only arterial structure is studied (e.g., using histology), whereas quantification of function in those same arteries could significantly improve insights. Furthermore, this set-up is potentially interesting for laboratory equipment producers to commercially produce and sell.

The constitutive modelling framework that we present in chapter 8 is aimed at attributing a change in arterial stiffness to one of the individual wall components. When e.g., developing a new drug to target arterial stiffness, such a model (our product) can be used to assess which component of the artery wall is affected by the drug. This methodology is truly innovative as it potentially allows clinical stiffness measurements to be used as more than “just” a single stiffness number. Besides this methodology, in chapter 12, we presented a novel set-up to study artery mechanics under pulsatile conditions. This set-up provides a methodology to fundamentally study arterial mechanics in pre-clinical, murine studies. Currently available methods are limited in the sense that they only allow for static measurements. Therefore, dynamic assessment of arteries provides an important step to study arterial mechanics under physiologically more realistic conditions.

Although our modelling methodology is potentially a candidate for valorisation, we plan to first further elaborate it before valorisation. During my follow-up research, I will continue to scrutinise and improve this methodology to verify the robustness of the results. An essential aspect of this verification process is an elaborate sensitivity analysis (see chapter 9), a technique which will be employed to quantify the validity and certainty of our model predictions. After these verification analyses, contact can be sought with medical device companies, of which Esaote Benelux (Maastricht, The Netherlands) is a potential candidate. Esaote is a leading manufacturer of medical ultrasound machines, and is a company with which we closely collaborate. Esaote has in the past always been open to new approaches that were developed in the academic sector.

Our set-up for pulsatile characterisation of artery mechanics, which is currently under further development, will deliver a highly relevant methodology for a large number of research groups at Maastricht University. Eventually, our set-up will be moved from the Department of Biomedical Engineering to the CARIM Muroidean Facility (CARIM-MF). CARIM-MF employs a group of highly skilled technicians that are experienced in working with small rodent models. The addition of our set-up to their laboratory will ensure that our methodology becomes accessible to all researchers at the CARIM School for Cardiovascular Diseases. Furthermore, researchers at other universities have shown interest in our methodology. A notable example is Prof. Jo de Mey at University of Southern Denmark (Odense, Denmark), whose focus is on human, small, resistance-sized arteries. Although physiologically these vessels are markedly different from the large arteries that our set-up is developed for, geometrically they are of the same size. This collaboration ensures

further development of our set-up towards clinical application.

Our pulsatile set-up could finally be produced and transferred/sold to third parties. We work in close contact with Danish Myo Technology (DMT, Aarhus, Denmark), a company producing laboratory equipment, in particular pressure myographs. For DMT, our pulsatile *in vitro* set-up would be potentially of commercial interest. In order to protect intellectual property rights, we will formulate a commercialisation roadmap in collaboration with the Technology Transfer Office (Maastricht Valorisation Centre) at Maastricht University. This roadmap will pinpoint exploitable aspects of our set-up, and will help identifying target markets, business conditions, opportunities and potential pitfalls.