



## Vascular robustness: The missing parameter in cardiovascular risk prediction<sup>☆</sup>

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### ARTICLE INFO

#### Keywords:

Cardiovascular diseases  
Risk factors  
Robustness  
Prevention

### ABSTRACT

Undetected high risk for premature death of cardiovascular disease (CVD) among individuals with low-to-moderate risk factor scores is an acknowledged obstacle to CVD prevention. The vasculature's functional robustness against risk factor derailment may serve as a novel discriminator of mortality risk under similar risk factor loads. To test this assumption, we hypothesized that the expected inverse robustness-mortality association is verifiable as a significant trend along the age spectrum of risk factor-challenged cohorts.

This is a retrospective cohort study of 372 adults (mean age 56.1 years, range 21–92; 45% female) with a variety of CV risk factors.

An arterial model (VascAssist 2, iSYMED GmbH, Germany) was used to derive global parameters of arterial function from non-invasively acquired pulse pressure waves. Participants were stratified by health status: apparently healthy (AH; n = 221); with hypertension and/or hypercholesterolemia (CC; n = 61); with history of CV event(s) (CVE; n = 90). Multivariate linear regression was used to derive a robustness score which was calibrated against the CVD mortality hazard rate of a sub-cohort of the LURIC study (n = 1369; mean age 59.1 years, range 20–75; 37% female).

Robustness correlated linearly with calendar age in CC ( $F(1, 59) = 10.42; p < 0.01$ ) and CVE ( $F(1, 88) = 40.34; p < 0.0001$ ) but not in the AH strata, supporting the hypothesis of preferential elimination of less robust individuals along the aging trajectory under risk factor challenges.

Vascular robustness may serve as a biomarker of vulnerability to CVD risk factor challenges, prognosticating otherwise undetectable elevated risk for premature CVD mortality.

### 1. Introduction

As the pandemic of chronic cardiovascular disease (CVD) accelerates, the UN has recently prioritized the goal of reducing premature CV mortality by 30% by 2030 (“WHO|NCD and the Sustainable Development Goals”, 2016). A prerequisite to achieving this target is the ability to detect the progressive impairment of CV function that causally precedes symptomatic disease manifestation (Taddei et al., 2003). However, the screening performance of all conventional risk factor models depends almost entirely on calendar age (CA) alone, such that the addition of all other biomarkers combined only marginally improves detection rates (Simmonds and Wald, 2012; Wald et al.,

2011). This uncertainty of prediction is the inevitable result of estimating an individual's disease risk using algorithms that have been derived from epidemiological cohort studies of biomarker-disease associations (Wald et al., 1999). Given the overlap of each biomarker's frequency distribution between sub-populations with and sub-populations without the disease, to be a useful discriminator of risk, each marker's association with CVD needs to be at least two orders of magnitude larger than what is typically observed (Pepe et al., 2004).

While this explains why the past 20 years of biomarker research have produced only marginal improvements to the risk factor models' predictive power (Folsom, 2013), it does not explain why, under a given risk factor ‘stress’, some people die prematurely whereas others

**Abbreviations:** AH, apparently healthy group; aoPWV, aortic pulse wave velocity; ATH, athletic group; BA, vascular biological age; CA, calendar age; CC, chronic condition group; CVD, cardiovascular disease; CVE, cardiovascular endpoint group; FMD, flow mediated vasodilation; PWV, pulse wave velocity; RCR, retrospective chart review; UN, United Nations; VA2, VascAssist 2

<sup>☆</sup> Subject Terms: Robustness, Biomarkers, Primary Prevention, Cardiovascular Disease

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<https://doi.org/10.1016/j.pmedr.2018.01.008>

Received 30 August 2017; Received in revised form 26 December 2017; Accepted 14 January 2018

Available online 28 January 2018

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are ‘robust’ enough to survive. Here we suggest that vascular robustness against risk factor stress is an important but unexplored parameter that may improve the risk factor models’ detection rates more substantially than additional biomarkers of risk.

Our rationale finds support in the recent suggestion that adopting insights of systems biology into risk evaluation may help us achieve the target of individualized prevention (Thomas and Lip, 2017). Incorporating principles of the sciences of complex systems, systems biology posits that biological systems display properties that can neither be predicted nor explained from the systems’ molecular constituents (Aderem, 2005; Kitano, 2002; Regenmortel, 2004). Termed ‘emergence’ this phenomenon is a fundamental property of all complex systems. Closely related to emergence is the phenomenon of robustness, a system’s ability to maintain a functional phenotype against a range of internal and external challenges and stochastic events (Kitano, 2007; Kitano et al., 2004; Stelling et al., 2004; Whitacre, 2012). Hence it is our intention to investigate robustness’ utility in risk prediction.

First, using plausible mechanistic parameters, we attempt to quantify the robustness criterion. We then use this criterion to formulate hypotheses that we test in a retrospective cohort study. We aim specifically at answering the question whether our proposed robustness criterion warrants the execution of more resource-intensive prospective studies that examine the predictive utility of robustness for efforts to reduce premature CVD mortality as demanded by the UN.

## 2. Methods

### 2.1. Parameterization of robustness

While the term robustness lacks a precise definition there is broad agreement that it encapsulates the maintenance of function against internal and external perturbations (Kitano, 2004; Rosenfeld, 2011; Whitacre, 2012). Here we conceptualize cardiovascular robustness as the CV system’s ability to maintain integrity of function against genetic variations, environmental challenges and stochastic events (Stelling et al., 2004).

The CV system’s function is to cushion the pulsatile left ventricular output into a constant blood flow, and to maintain that flow to all tissues and cells in accordance with their nutritional, energetic and waste disposal needs. Being essentially a hydraulic system that consists of a pulsating pump (heart) and elastic tubes (arterial segments), the parameterization of the cardiovascular system’s functional properties requires reference to the laws of physics. This dependence of flow and pressure on compliance, resistance and inertia is evident in the Hagen-Poiseuille and Moens-Korteweg equations which allow for the mathematical description of arterial vascular function.

Based on the electric-hydraulic analogy this system has been represented by networks of electronic circuits (Chen et al., 2014; Olufsen and Nadim, 2004; Stergiopoulos et al., 1999; Westerhof et al., 1969), in which the passive elements of resistance, capacitance and inductance represent their hydraulic equivalents of resistance, compliance and inertance.

Given the importance of vascular function as a benchmark of cardiovascular health, calls have been made to develop methods that provide a non-invasive assessment of all these parameters as the determinants of vascular function (Thijssen et al., 2015; Tomiyama and Yamashina, 2010).

Correspondingly, a recently developed system (VascAssist 2, iSYMED GmbH, Germany) applies the electronic-hydraulic analogy to a model of the arterial tree which consists of 721 electronic circuits representing central and peripheral arterial sections. By modulating the circuits’ capacitance, resistance, inductance, voltage and current the system replicates a person’s non-invasively acquired pulse pressure wave, thereby uncovering the arterial functional parameters that generated the wave in the biological original. The system is described in Appendix A.

### 2.2. Quantitation of robustness

Robustness, as conceptualized above, acts as an effect modifier to the biomarkers of risk to which an individual is exposed. Only if this effect modification is large enough to become measurable by a significant modification of CA - the risk factor models’ dominant marker -, will robustness be useful for risk stratification. Consequently, it makes sense to express robustness in units of years to quantify its impact on the age-mortality association. The resulting difference between calendar age and the robustness-corrected age represents the vascular robustness score, which, from here onwards, is referred to as *delta age*. The algorithms that we developed to derive the parameters and dimensions of robustness from the data supplied by the VA2 system are hereinafter summarily referred to as *vasometrix*.

### 2.3. Hypotheses

We test the following two hypotheses: when stratified by degree of biomarker stress (non-age risk factors) into healthy and exposed strata, the exposed population strata will show a significant positive correlation between robustness and CA (hypothesis A). The robustness-CA correlation in the exposed strata will be significantly stronger than the correlation in the unexposed stratum (hypothesis B). Hypothesis A emerges from the rationale that individuals with lower robustness will be subject to preferential elimination (premature mortality) such that older cohorts are relatively “depleted” of these less robust individuals. Hypothesis B is founded on the assumption that robustness acts predominantly as an effect moderator of non-age risk factors.

### 2.4. Study population & data acquisition

This study is a retrospective chart review (RCR) of a cohort of 410 adults (mean age 56.1 years, range 21–92; 45% female; from here on referred to as the vasometrix cohort) with a variety of CV risk factors. Appropriately sized inflatable cuffs were used for acquisition of the pulse pressure curves using the oscillometric VA2 device. The participants rested supine for 15 min before pressure measurements were obtained. Measurements were performed in triplicate at the brachial and radial arteries. Sampling frequency was 1 kHz.

### 2.5. Inclusion and exclusion criteria

A replication fidelity of simulated PP curves vs. sampled curves of  $\leq 97\%$  (for definition of fidelity see Appendix A), and/or age < 21 years served as the exclusion criteria. We excluded (a) 36 of the 410 participant records for reasons of inadequate replication fidelity, and (b) another 2 records of participants with resting tachycardia (HR > 100 beats per minute, a > 3 SD difference from the cohort mean). All records that were not explicitly excluded by these criteria were included.

### 2.6. Confidentiality and ethical considerations

All data had been recorded and processed such that subjects cannot be identified.

This RCR was conducted in conformance with the Declaration of Helsinki and under the approval of the local ethics committee (Ethikkommission des Saarlandes, 66111 Saarbrücken/Germany).

### 2.7. Statistical analyses

The study cohort was first divided into three main groups: apparently healthy (AH;  $n = 221$ ), with hypertension and/or hypercholesterolemia but without having a history of CV events (CC;  $n = 61$ ), with history of CV event(s) which we defined as a history of myocardial infarction, stroke or heart failure (CVE;  $n = 90$ ). Given the known

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