$p < 0.001$; and group 4: 11.53 ± 2.22 m/s vs. 13.17 ± 1.54 m/s; $p < 0.001$) (**Figure 1**). In multivariate regression analysis, PWV was independently related to age group ($b = 0.61$; $p < 0.001$), mean BP ($b = 0.29$; $p = 0.001$), heart rate ($b = 0.23$; $p = 0.006$), and creatinine ($b = 0.19$; $p = 0.01$); (R^2 of the model: 0.59).

In the present study, we assessed aortic stiffness in a population with high rates of longevity. Aortic stiffness increases gradually with age; however, at >50 years of age, aortic stiffening seems to be decelerated because the measured PWV was significantly lower than reference values. This finding may be attributed to either a favorable hemodynamic pattern (progressive increase in systolic BP with age, but stable diastolic BP at older ages—an excessive decrease of diastolic BP hampers coronary flow) or to beneficial genetic and metabolic backgrounds that are implicated in the process of both longevity and aortic stiffness. The favorable lipid profile and the relatively low percentage of smokers among the elderly may have contributed to the results (4). Moreover, previous results from the IKARIA study showed a favorable effect of physical activity on endothelial function, which may be related to attenuated aortic stiffening (1). Hereditary aspects of aortic elasticity may also play a role given the evidence that paternal longevity is associated with decreased PWV in offspring (5).

The cross-sectional nature of our study does not allow for conclusions regarding causality, and selection bias may have interfered. Whether this privilege of aortic mechanics can also be extended to the younger generations living in the particular island is a hypothesis that needs further investigation. Finally, aortic imaging modalities that provide structural information could have enhanced our results.

Whether aortic stiffness retains its established predictive value with increasing age is an intriguing issue, with most studies attesting to an incremental predictive ability even at older ages. Given the adverse prognostic impact of aortic stiffening on cardiovascular and total mortality, the present findings may imply a possible link between longevity and aortic stiffness.

*Panagiota Pietri, MD
Charalambos Vlachopoulos, MD
Christina Chrysohoou, MD
George Lazaros, MD
Konstantina Masoura, MD
Nikolaos Ioakeimidis, MD
Dimitris Tousoulis, MD
Christodoulos Stefanadis, MD

*1st Cardiology Department
Athens Medical School
Hippokration Hospital
Kythnou 15, 15231
Athens
Greece
E-mail: panpietri@hotmail.com

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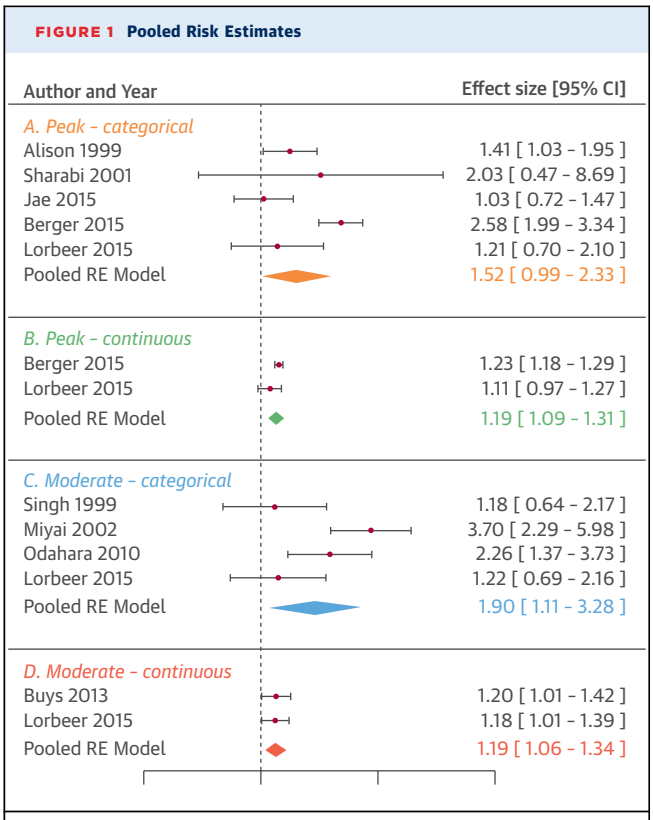
Clinical Relevance of Exaggerated Exercise Blood Pressure

Exercise stress testing is routinely used to assess cardiovascular risk, and measurement of blood pressure (BP) during the test is a standard component of patient monitoring (1). Irrespective of whether BP is considered normal at rest (in-clinic BP <140/90 mm Hg), some individuals may experience abnormal (hypotensive or hypertensive) BP responses during exercise testing. Our recent meta-analyses demonstrated that abnormal BP responses carry significant risk for future cardiovascular events and mortality, independent of resting BP and other cardiovascular risk factors (2,3). Although exercise hypotension is a sign of significant cardiovascular pathology, it is possible that some of the cardiovascular risk associated with exercise hypertension (exaggerated exercise blood pressure [EEBP]) relates to underlying (masked) hypertension (4) gone unnoticed with clinic BP screening, or to future development of overt hypertension detectable with in-clinic BP screening. A pooled summary of studies assessing the relationship between EEBP and incident hypertension has never been undertaken, and is an important step with respect to determining whether EEBP has utility for early identification of people at heightened cardiovascular risk. Therefore, we sought to conduct a systematic review and meta-analysis to determine



Pooled risk estimates from 9 studies (adjusted for resting BP, age, sex, and other cardiovascular risk factors) for the association between exaggerated exercise blood pressure (EEBP) and incident hypertension. Risk estimates for incident hypertension were pooled by EEBP defined in 4 ways; **A**: at peak exercise intensity on a categorical scale **(orange)**; **B**: on a continuous scale **(green)**; **C**: at moderate exercise intensity on a categorical scale **(blue)**; and **D**: on a continuous scale **(red)**. All pooled analyses show that EEBP (systolic BP) was associated with significantly increased risk for incident hypertension. BP = blood pressure; CI = confidence interval; RE = risk estimate.

associations between EEBP and incident hypertension among people with normal resting BP at baseline examination.

We searched 7 online databases for studies measuring dynamic exercise BP that reported incident hypertension (defined from clinic BP ≥140/90 mm Hg) among those normotensive at baseline. Random-effects meta-analysis was applied to pool risk estimates (RE) for incident hypertension on the basis of EEBP defined from the systolic BP during exercise (at moderate or peak intensity), or as the change in systolic BP from rest. Data was analyzed comparing RE on categorical (those with vs. those without EEBP) or continuous (per 10 mm Hg increase) scales.

Quantitative RE were extracted for meta-analysis from 16 studies that met the inclusion criteria, with a total of 23,207 participants (mean age 42.4 ± 7.1 years), followed for 5.3 ± 2.1 years. Several meta-analyses were performed on the basis of different definitions of EEBP. Pooling RE from 5 studies defining EEBP at peak exercise intensity and 4 studies at moderate exercise intensity (adjusted for resting BP, age, sex, and other cardiovascular risk factors), revealed that EEBP (systolic BP) was associated with significantly increased risk for incident hypertension when compared with those without EEBP (Figure 1). Similarly, each 10 mm Hg increase in exercise systolic BP at peak (pooling 2 studies) and moderate (pooling 2 studies) exercise intensity was associated with increased risk of incident hypertension (Figure 1). When pooling 3 studies defining EEBP by change in systolic BP from rest to peak exercise intensity, EEBP was associated with greater risk for incident hypertension (RE: 1.98 [95% confidence interval (CI): 1.19 to 3.31], $I^2 = 62.0\%$) compared to those without EEBP. Further pooling of 9 studies that reported RE unadjusted for resting BP or other cardiovascular risk factors (7 from EEBP defined during peak exercise, 2 from EEBP defined at moderate) revealed similar, positive associations between EEBP and incident hypertension (RE: 1.97; [95% CI: 1.57 to 2.46], $I^2 = 56.9\%$ and RE: 2.26; [95% CI: 1.60 to 3.20], $I^2 = 16.7\%$, respectively).

This is the first meta-analysis to demonstrate that EEBP predicts incident hypertension independently of in-clinic resting BP and other cardiovascular risk factors. This analysis provides evidence to support the clinical value of EEBP to detect cardiovascular risk related to BP that would remain otherwise undetectable by conventional (resting) BP measurements. Millions of clinical exercise stress tests are conducted worldwide every year, with BP as a standard measurement. Our findings suggest that EEBP should alert supervising physicians to a heightened level of cardiovascular risk associated with BP, and this should warrant further investigation with respect to BP control and/or lifestyle intervention.

Martin G. Schultz, PhD
Petr Otahal, GDipAppStat
Dean S. Picone, BMedRes (Hons)
***James E. Sharman, PhD**

*Menzies Institute for Medical Research
University of Tasmania
Private Bag 23
Hobart, 7000
Australia
E-mail: James.Sharman@utas.edu.au

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What Is the True Prevalence of Hypertrophic Cardiomyopathy?

In a recent paper by Semsarian et al. (1), several arguments are presented indicating that the prevalence of clinically expressed and hypertrophic cardiomyopathy (HCM) gene carriers has been greatly underestimated and could be as high as 1:200. This updated frequency estimate was primarily on the basis of a genetic analysis, published in 2012, that demonstrated 22 of 3,600 participants from the Framingham Heart Study and Jackson Heart Study cohorts had likely pathogenic or pathogenic sarcomeric gene variants (2). Although Semsarian et al. (1) stated that the variants were classified "using stringent criteria for pathogenicity," it is important to note that since 2012, there have been significant advancements in the tools to aid in variant classification (i.e., determining whether a variant is benign or pathogenic).

Technological advances have allowed us to more comprehensively and efficiently interrogate human genomes, and there are a number of large-scale efforts, such as the Exome Sequencing Project and Exome Aggregation Consortium, which have been publishing genomic data and variant frequencies from very large populations stratified by ethnicity. These large-scale efforts are important for variant classification because they provide population minor allele frequencies that, when used in concert with disease prevalence estimates, may push a variant into a benign or pathogenic category. Furthermore, databases such as ClinVar (3) and Human Genome Mutation Database make it easier for us to access variant classifications and publications by different clinical laboratories and groups. Variant data, from even just a few short years ago, should be reviewed through the lens of these new resources, and revisited accordingly, in this rapidly changing landscape.

As such, we took a closer look at the 22 variants classified as pathogenic or likely pathogenic by Bick et al. (2). The vast majority (20 of 22) of these variants were missense variants, which tend to be less straightforward to classify. Interestingly, only 4 of the 22 individuals actually expressed HCM (but were not specified by Bick et al. [2]). Utilizing our criteria for variant classification, which is largely on the basis of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology 2015 guidelines for variant interpretation (4) and utilizes databases and resources listed in the preceding text, only 6 of these variants could be confidently classified as likely pathogenic or pathogenic (i.e., 6 of 3,600, or approximately 1:600 HCM gene carrier frequency). In viewing ClinVar data, we observed that the Harvard Laboratory for Molecular Medicine (whom participated in the original Bick et al. [2] variant classification) currently classifies 12 of the 22 variants as variants of uncertain significance (equating to an HCM gene carrier frequency of 1:360).

Assessment of these 22 variants illustrates the somewhat subjective and rapidly evolving nature of genetic variant classification. After applying contemporary variant classification strategies to the 2012 data, the resultant data would not support a frequency as high as 1:200. Rather, it would seem to continue to support the 1:500 frequency of the disease more prevalently referenced in the published data. This frequency would take into account reduced penetrance (i.e., gene-positive, phenotype-negative cases), as well as HCM cases with nongenetic causes. With that said, these numbers will likely continue to change as our variant interpretation strategies continue to evolve. More standardized variant classification criteria would be helpful and improvements in that area have been made (3,4). However, the complexities of variant classification will likely continue to leave this field somewhat in flux, and the example with HCM presented here is likely just the tip of the iceberg.

*Linnea M. Baudhuin, PhD
Katrina E. Kotzer, MS, CGC
Michelle L. Kluge, MS, CGC
Joseph J. Maleszewski, MD

*Mayo Clinic
Laboratory Medicine and Pathology
200 First Street SW
Rochester, Minnesota 55905
E-mail: baudhuin.linnea@mayo.edu

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