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CASE REPORT

Managing Refractory Hypertension: A Case Study Exploring the Influence of ACE and ACTN3 Gene Polymorphisms

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Abstract: The responses to Antihypertensive drugs vary among patients. The renal and muscular processes of blood flow regulation in peripheral blood vessels depend on the genetic and physiological constitution. Here, we present a case of an elderly female patient who experienced several phases of hypertensive emergencies during supervised training sessions. Hypertension treatment with different ACE inhibitors was discontinued because of severe side effects or simply no effect. Genotyping of ACE and ACTN3 gene polymorphisms helped find adequate antihypertensive treatment after all other approaches failed. The measured ACTN3-RR genotype indicated the possibility of a higher proportion of fast-twitch muscle fibers. This type of muscle fiber contributes to the generation of a high muscle force, which can compress the vascular bed more during physical work than slow muscle fibers. Therefore, a beta-blocker was used for treatment, allowing better vasodilative capacity. As reported by the patient, this pharmaceutical alone helped treat hypertensive emergencies adequately. Therefore, we believe that genetic information can help to identify optimal pharmaceutical treatments a problem that is highly prevalent in elderly subjects.

Keywords: muscle fiber composition, mitochondrial content, renin-angiotensin aldosterone system

Introduction

First evidence of genetic polymorphisms influencing human physical performance and cardiovascular functioning/health is already reported in the 1990s for ACE gene.[1–3] The ACE insertion/deletion (ACE-I/D, rs1799752) polymorphism has been associated with performance and exercise capability in various populations.[4,5] In fact, many metabolic affections are related to predominantly the ACE I/D gene polymorphism and affected cardiovascular regulation. This includes, hypertension, Type 2 Diabetes Mellitus, Diabetic Nephropathy, Dyslipidemia, Metabolic Syndrome, Cardiovascular Diseases Hypertonia, Polycystic Ovary Syndrome.[6,7] These disease associations which are driven by the ACE-DD genotype, are often population-specific and influenced by environmental factors such as diet, altitude, and physical activity.[6,7] Thereby, especially hypertonia is highly present in elderly subjects making this problem a serious issue for medical treatment with often challenging situations for the general practioner to help suffering patients.

The I allele, which represents a insertion of 287bp, is associated with lower serum[8] and tissue[3] ACE activity, and improved performance in endurance sports. The deleted form of the variant (D allele) is associated with higher circulating and tissue ACE activity.[9] Furthermore, enhanced performance in sports that require high cardiovascular output and muscle perfusion during short bursts of power, such as sprinting or hopping, is associated with the D allele.[9] ACTN3 has been well studied as a target gene for human performance, especially at the skeletal muscle level.[10,11] The ACTN3 gene encodes actinin-3, which is almost exclusively expressed in the sarcomere of fast glycolytic type II fibers that are responsible for the generation of rapid forceful contractions during activities such as sprinting or weightlifting.[10,11] As XX genotypes of the ACTN3 polymorphism are associated with a shift toward oxidative muscle

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phenotype, which typically exhibits higher capillary density, and these genotypes may show enhanced angiogenic signaling (eg, VEGF expression) in response to endurance training, potentially supporting greater microvascular density.[10,11] Furthermore, as a deficiency of ACTN3 protein yields to a lower ability to contract skeletal muscle as the Actinin-Myosin connection is less rigid, higher forces can be produced in subjects having an ACTN3 polymorphism, as these have this specific protein allowing them to produce higher functional forces measurable for example with maximum torque production.[10,11] To point out, both clinical and experimental evidence supports the hypothesis that genetic variation within the renin–angiotensin–aldosterone system (RAAS) contributes significantly to the development of hypertension and mediates variability in both peripheral and central blood pressure regulation in response to antihypertensive treatment. With regard to ACE-I/D polymorphisms and their implications for therapy, several studies underscore genotype-specific effects. For instance, Lee et al (1995) explored the influence of ACE-I/D polymorphism on the response to enalaprilat but found that, in a relatively small sample (n=54), the effect did not reach statistical significance.[12] However, subsequent research by Hingorani et al (1995) provided evidence that both the ACE-I/D and angiotensin receptor 1 A1166→C polymorphisms independently predict treatment of systolic and diastolic blood pressure, with indications of interaction between the loci.[13]

Further clinically relevant genotype-dependent effects have since been reported. Ha et al (2000) demonstrated that patients with the ACE-DD genotype showed a more pronounced antiproteinuric response to ACE inhibitors in the context of non-insulin-dependent diabetic nephropathy.[14] Similarly, Gupta et al (2015) reported a significant association between ACE-I/D genotypes and blood pressure response to ramipril in hypertensive patients treated in conjunction with diuretics.[15] Importantly, gene-treatment interactions appear to be modulated by environmental and ethnic factors. The impact of ethnicity on the expression and effect of the ACE-I/D polymorphism has been substantiated in multiple studies.[16–18] This variation may partly explain the reduced responsiveness to ACE inhibitors observed in some individuals of African descent.[19,20] Furthermore, population-based studies indicate that the association between the ACE-DD genotype and essential hypertension is more pronounced in certain ethnic groups, such as Indian, Japanese, and Mongolian populations, while being less consistent in others, including Belgian, Dutch, and Bangladeshi cohorts.[19,20]

Additional RAAS-related variants, including rs4359 within the ACE gene, also affect the pharmacodynamics of ACE inhibitors, whereby a co-dominant influence of this SNP on ramipril-induced blood pressure reduction was reported.[21] These studies collectively support the notion that pharmacogenetic profiling, including ACE and other RAAS related gene polymorphisms, holds promise for stratifying patients and optimizing antihypertensive treatment outcomes.[21]

Homozygous ACE II genotypes are especially associated with lower ACE activity and consequently reduced concentrations of angiotensin II, the main vasoconstrictor (reviewed in[22] and[23]) an effect of modifying human performance. It has also been shown to have lower angiotensin II levels, resulting in higher blood pressure values under stress.[24] This effect shows the complexity and interdependency as Homozygous ACE II genotypes have in tendency a higher heart rate under stress derogating the mentioned first effect.[25–27] Interaction effects are implied and it should be emphasized that intense exercise elevate serum concentration of angiotensin 2.[28] Interactions with the type of stimulus are also suspected, whereby individuals with a fast muscle fiber type can develop higher forces in the skeletal muscle than individuals with a slow muscle fiber type.[10,11] The reason for this seems to be that the higher forces produced by fast muscle fibers compress the capillary bed harder and thus result in a secondary surge in blood pressure compared with the force produced by slow-twitch type I muscle fibers.[29]

The Case

After informed consent for publication was obtained, we present here a case of a 73-year-old patient (1.67 cm / 52 kg) diagnosed with heart failure with preserved ejection fraction. The patient also had mild mitral insufficiency. In detail: Normally sized left ventricle, not yet hypertrophied (but with concentric remodeling), with normal global systolic function (left ventricular ejection fraction 75%) without indication of regional wall motion abnormalities, diastolic dysfunction with signs of elevated left ventricular enddiastolic pressure (LVEDP) without indication of regional wall motion abnormalities, diastolic dysfunction with signs of elevated LVEDP, slight dilation of the left atrium, normal dimension of the right atrium, normal dimension and function of the right ventricle, tricuspid aortic valve, edges slightly sclerosed, no central insufficiency, normal valve opening movement, no stenosis. Mild to moderate mitral insufficiency

with slight prolapse of the posterior mitral leaflet. Minimal tricuspid insufficiency. Above the TI, a systolic pulmonary arterial pressure of 22 mmHg was calculated. Inferior vena cava not congested, collapses more than 50% during inspiration. No pericardial effusion. In a 24h blood pressure measurement mean blood pressure values of 139/74 mmHg were detected, with an average of 127/70 mmHg during night respectively sleeping phases.

The patient was trained under supervision during a longer period which she experienced several hypertensive emergencies. Her medical history revealed further details: the cardiologist performed several 24-hour blood pressure measurements, and the patient received comprehensive cardiological care. First, treatment was carried out with the help of an ACE inhibitor (Coversum), which the patient tolerated very poorly, in line with descriptions of episodes of malaise during physical exertion under treatment with this pharmaceutical.[30] Changing to other pharmaceuticals, such as AT1-Antagonists, Calcium-Antagonists, Aldosterone antagonists, nitrats, and moxonidin, was not helpful, and hypertensive crises developed repeatedly. Because of persistent hypertensive attacks, genotyping was carried out and it was revealed that the Patient has a heterozygous form (an ACE I/D genotype), or a heterozygous deletion in the ACE gene, in combination with a genetic influence towards a fast muscle fiber type with a homozygous ACTN3-CC genotype. The measured ACTN3-CC genotype in the patient indicates the possibility of a higher content of fast muscle fibers.[18,29,31] However, the work performed in the performance test (RER max = 1) was very low at 73 watts, which was still aerobic. The maximum oxygen uptake capacity of 1.2 liters is very low; therefore, the person probably has insufficient metabolic reserves or capacity to support higher muscle performance. This includes an insufficiently developed capillary bed in peripheral muscles. Her fast muscle fiber type II phenotype probably accentuated and perpetuated the lack of a sufficient capillary bed. It should also be mentioned that based on the near-infrared spectroscopic measurement conducted during spiroergometry,[27] the immediate drop in hemoglobin concentration and oxygen saturation under stress only showed a slow desaturation. As oxygen desaturation matches muscle respiration rates,[32] this information illustrates the hypothesis of a problem in the skeletal muscle.

Summary Assessment and Therapeutic Procedure

The patient experienced repeated phases of hypertensive emergencies during supervised training and at home. Hypertension was finally treated with a beta-blocker despite the widespread consensus that beta-blockers are not indicated as a first-line treatment for hypertension.[33] Beta-blockers not only lowered the heart frequency but also widened the vascular bed, which probably explains the good effect of this medication in her case with the indicated problem of deoxygenation, as shown in Figure 1. As this was the only medication that the patient ultimately tolerated reasonably well, it was recommended that she continue to take it. Based on the genetic analysis, ACE and ACTN3 gene polymorphisms are prominent if not most prominent genetic regulators of the physiology of the blood pressure system respectively skeletal muscle, it could be deduced that the heterozygous form of ACE-I/D, which is codominantly expressed, explains part of the patient's hypertensive emergencies. Owing to the repeated problems with ACE inhibitors, they should no longer be used in antihypertensive therapy. Historically, the partially missing effect of ACE inhibitors was resolved after the 1990s using a heuristic approach of rotating a combined medication.[34] Since the mid-1990s, allelic variations in ACE have only been known to contribute to up to 37% of individual fluctuations in blood pressure.[35] Furthermore, due to the fast muscle fiber type mentioned, there is a genetic predisposition that promotes occlusion of the capillary bed in the contracting muscles and thus cannot be ruled out as a causal factor in hypertension. In summary, beta blockers, which are known to have vasodilatory effects, may be a useful alternative treatment. Furthermore, as indicated by Figure 2, deoxygenation was poor, and therefore, a problem in the capillary bed must exist. Therefore, pruning of the microvascular tree increases peripheral resistance[23] and the reactivity or capacity for cardiovascular perfusion in the peripheral muscle tissue. Aerobic exercise training has particularly positive effects on the capillary bed, which may be refined with metabolically eccentric protocols, as these increase microvascular perfusion.[36–38] Kneipp therapy to optimize vessel reactivity is not very stressful and would probably have very good effects on this patient with severely limited cardiopulmonary fitness.[39]

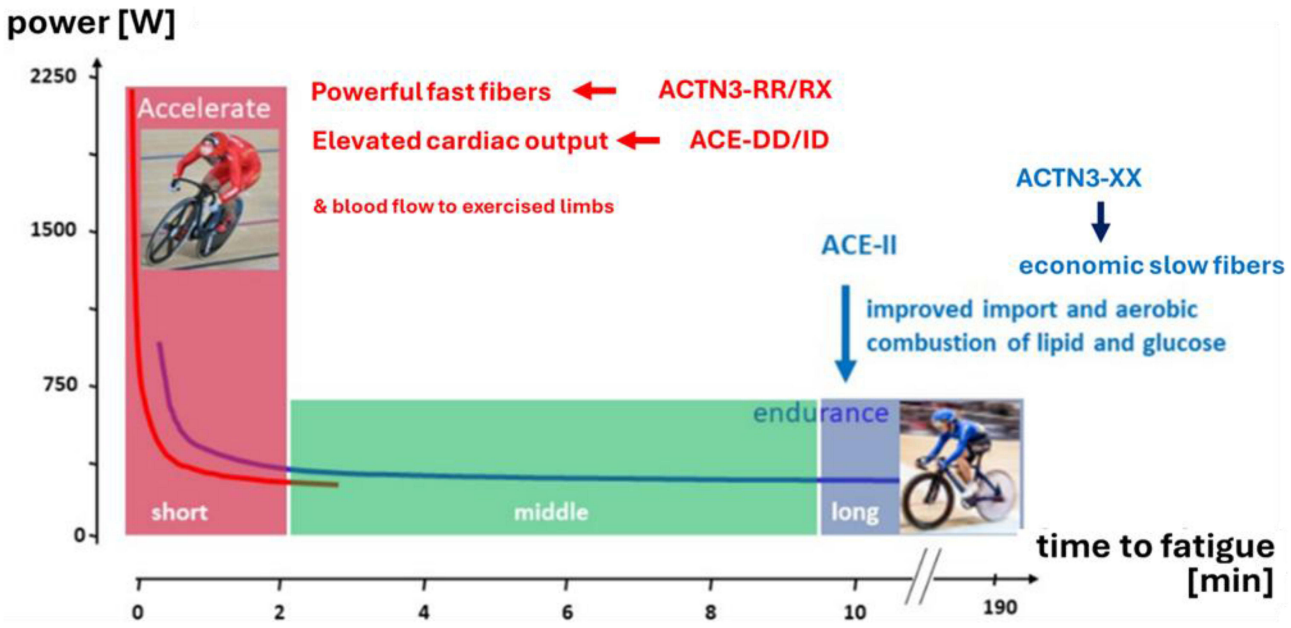

Figure 1 Points of inference of ACE and ACTN3-gene polymorphisms on power output during endurance performance.
Notes: Assembled drawing of the hyperbolic relation between maximal power output and the duration of sustainable muscle work at maximal intensity with a superimposed indication of the implicated mechanism affected by the studied genotypes of the ACE and ACTN3 gene polymorphism. (Data are drawn according to Flück[40]) based on a mean body weight of 75 kg and a biomechanical efficiency of 25%. In otherwise non-symptomatic subjects, the condition of ACE DD and ACTN3-RR represent a relative advantage for maximal performance during short, mostly anaerobic, exercise performance whereas ACE II and ACTN3-XX genotypes are of an advantage for fatigue resistance during aerobic exercise.

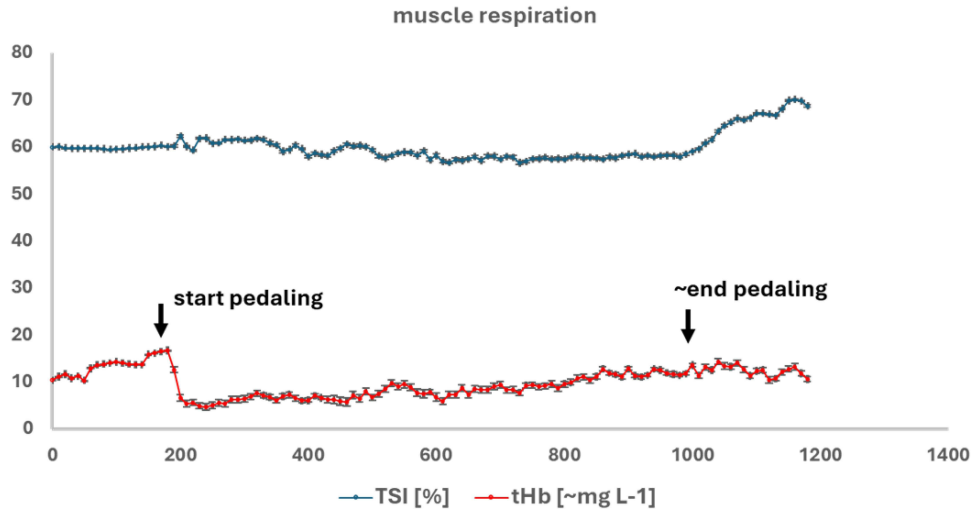

Figure 2 Abnormal impact of cycling exercise on muscle respiration in the patient.
Notes: Line graph depicting muscle oxygenation (as a measure of muscle respiration) and hemoglobin content during the performance test of cycling exercise. Tissue saturation index (TSI) and hemoglobin in knee extensor muscle during cycle ergometry are given as mean and standard error of measures over 10-seconds intervals (sample rate 10 Hz). Arrows indicate the time points when pedaling started and ended. Note that there is no reduction in TSI as would be expected from the activation of aerobic metabolism and the accruing oxygen deficit. The maximum performance achieved was 73 Watt, which is 1.4 Watt per kg body mass and has to be taxed as very low).[19]

Conclusions and Outlook – Development of a Gene-Physiologically Based Prognosis for the Optimized Treatment of Hypertension

Diseases of the cardiovascular system (CVD) lead to most deaths annually, often starting with hypertension. CVD causes irreversible damage to organisms in the medium to long term. Thereby, current treatment almost always consists of pharmaceutical intervention, and if tolerated and carried out by the patient, physical exercise. The response to a particular

antihypertensive drug varies greatly, and is often insufficient to treat cardiovascular complaints. Therefore, current treatment is mostly based on a heuristic procedure in which drugs are administered according to the trial-and-error principle. This leads to an uncertain treatment outcome and is potentially harmful owing to the toxic side effects of inefficient pharmaceuticals, rendering treatment more expensive without patient benefit. A promising solution could involve the clinical implementation of research results on environmental genotype-phenotype interactions in the last few decades. Research indicates that the inefficiency of ACE-targeted antihypertensive drugs and physical activity can be explained by individual differences in the expression of biological variables of cardiovascular function and aerobic metabolism in association with the ACE-I/D genotype.[41–43] Specifically, renal and muscular processes of blood flow regulation in peripheral blood vessels are crucial elements of blood pressure control during physical activity, depending on genetic and physiological constitution.[4,26,27,44,45] Therefore, according to other reports, ACE-inhibition-related hypotension during muscle work may occur frequently.[30] This indicates that it may be worthwhile to engage in a proactive evaluation of the genetic and muscle-physiological constitution of patients with hypertension who do not or adversively respond to the first or second choice of treatment targeted at inhibiting the RAS system (ie, ACE and angiotensin receptors). Technical advances in physiological and genetic diagnostics, together with the knowledge available today, allowed us to draw a priori conclusions on the optimal combination of medicinal and exercise stimuli for improved BP control of blood pressure. The current challenge is to integrate the available quantitative information (on the interdependent impact of genetics, exercise stimuli, and pharmacology) to implement an operationalizable routine for personal-centered anti-hypertensive therapy.

To point out, current evidence from pharmacogenetic research and clinical trials indicates that in patients exhibiting suboptimal or absent responses to antihypertensive pharmacotherapy, it is both reasonable and increasingly feasible to investigate the influence of genetic variants affecting the drug's targeted pathways. As hypertension is a multifactorial disorder arising from the interplay of genetic, environmental, and lifestyle influences. With over 900 loci linked to blood pressure regulation.[46,47]

This mosaic pathogenesis calls for integrative strategies combining genomics, environmental risk profiling, and behavioral interventions to optimize prevention and management.[47] Nevertheless, the ACE-I/D polymorphism has been found firmly associated with differential response to physical exercise and second-generation ACE inhibitors, particularly under conditions of increased cardiovascular demand such as physical activity when also the ACTN3 gene polymorphism intervene possibly via affecting central hemodynamic function (ie cardiac output) or peripheral resistance.[25] Identification of these variants may provide a mechanistic explanation for individual variability in drug efficacy and support more personalized, effective, and safer intervention strategies. Furthermore, depending on the clinical phenotype, genetic screening may be broadened to encompass additional components of the renin-angiotensin-aldosterone system (RAAS), including the ACE haplotype and the bradykinin axis, particularly in cases where compensatory regulatory mechanisms are suspected to attenuate therapeutic effects.[48] Advances in next generation sequencing and PCR validation have now made these analyses both technically viable and clinically applicable, as required by medical regulatory standards. Thereby, to better assess the contribution of the ACE-I/D polymorphism to cardiovascular functional impairment and treatment response, it is critical to consider the heterogeneity of published findings in light of overlooked modulatory factors. Chief among these are ethnic background, environmental conditions (eg, temperature, hypoxic exposure), and habitual physical activity levels—all of which shape RAAS activity and may confound genotype-treatment outcome relationships.[28,49,50]

Thereby, large-scale studies such as GenHAT[51] aggregated data from ethnically diverse populations may have inadvertently masked genotype specific treatment effects by not stratifying for such key confounders. These methodological limitations may have contributed to the widespread perception that the predictive value of the ACE I/D polymorphism is limited when considered in isolation. There is a compelling need for novel research frameworks and translational paradigms to unlock the full clinical utility of pharmacogenetic insights.[52] Looking ahead, an integrative approach that combines molecular genotyping with functional cardiovascular phenotyping including parameters such as cardiac output, VO_2 kinetics, and muscle oxygenation during exertion may offer a higher-resolution understanding of individual drug response. Naturally this may also weigh the evidence for the different impact of selection pressure on the blood pressure regulation.[19,20] Such a systems-level perspective on the RAAS could help guide the tailored use of antihypertensive medications in patients with genotype-specific regulatory dynamics. Thereby, future research should focus on prospective, larger-scale cohorts or randomized controlled trials that systematically assess the independent

contributions of ACE and ACTN3 polymorphisms, and detailed physiological characteristics, to individual patient antihypertensive therapy. These forecasted studies are needed to authenticate these findings and understand the applicability and clinical value of this comprehensive approach across population groups. Even with the so improved evidence it still remains challenging to institutionalize the proposed approach in a cost-effective and easy practical manner.

Institutional Review Board Statement

We acknowledge the institutional approval of the local ethics commission for the study and publication of the case details. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the local ethics committee by general consent (Ethics commission of north-eastern Switzerland).

Informed Consent Statement

Informed consent was obtained from the person described and the consent for publication has been obtained from the patient.

Data Sharing Statement

Data is available upon reasonable request from the corresponding author.

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Disclosure

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