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Cardiovascular pharmacotherapy: Innovation stuck in translation

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Systematic reviews of animal studies have revealed serious limitations in internal and external validity strongly affecting the reliability of this research. In addition inter-species differences are likely to further limit the predictive value of animal research for the efficacy and tolerability of new drugs in humans. Important changes in the research process are needed to allow efficient translation of preclinical discoveries to the clinic, including improvements in the laboratory and publication practices involving animal research and early incorporation of human proof-of-concept studies to optimize the interpretation of animal data for its predictive value for humans and the design of clinical trials. Illustrated by recent clinical trials in the area of (cardiac) ischemia-reperfusion injury performed by this author and his colleagues, the impact of translational problems between animals and humans will be discussed on clinical development of therapeutics.

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Angiotensin-converting enzyme insertion/deletion polymorphism in hypertrophic cardiomyopathy: An Egyptian case control study

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Introduction: Hypertrophic cardiomyopathy exhibits highly variable clinical profile. Sarcomeric gene mutations are known as a common cause in disease etiology. However, modifier genes are proposed to contribute to the disease expression. Polymorphisms in genes encoding the renin-angiotensin-aldosterone system are plausible candidate modifiers. The insertion/deletion (I/D) polymorphism of the ACE gene has been shown to predict about half of the inter-individual variability in the serum and tissue levels of the ACE enzyme. The ACE enzyme activity was reported to be highest in DD genotype, intermediate in ID and lowest in II individuals. In this study, we examined the potential relationship between ACE I/D polymorphism and HCM in an Egyptian case control study.

Materials & Methods: We examined 203 healthy adult control subjects and 211 genetically unrelated HCM patients -screened for mutations in three sarcomeric genes; MYBPC, MYH7, TNNT2 for the ACE I/D polymorphism. Patients were assessed for their clinical and echocardiographic parameters (determination of LVMI and Wigle's score was performed whenever possible).

Results: The D allele frequency was found to be similar between HCM cases and healthy subjects (0.68), and is among the highest reported frequencies in other populations. The HCM cases showed a statistically significant higher frequency of DD genotype compared to control subjects (P=0.04). Furthermore, the DD genotype was significantly higher among the sporadic HCM patient group compared to familial cases (P=0.0001). The ACE I/D genotype status did not reveal significant correlation to the pattern of disease expression (both clinically and echo cardio-graphically).

Discussion: This study on a large sample size to determine the role of the ACE polymorphism in HCM is useful to compensate for effects of other modifiers. ACE I/D polymorphism did not correlate with disease expression of the studied cases. However, further studies on the modifying effect of this variant within extended families may show a contributing role of ACE I/D variant to disease expression in a relatively homogeneous genetic background. Study of additional potential modifiers may show a synergetic effect on HCM variable expressivity. Our observation on ACE genotype distribution among the studied cases suggests that HCM expression particularly among the sporadic cases, is partially influenced by a genetically predisposed milieu.

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