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Reply to: MS #200906019, Yu H, et al., Whether B-type Natriuretic Peptide or Its Gene Polymorphism Predicts Patient's Outcome after Coronary Artery Bypass Graft Surgery?

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We appreciate Dr. Yu *et al.*'s interest in our April, 2009 publication in which we describe significant associations between single nucleotide polymorphisms (SNPs) within the natriuretic peptide *NPPA*, *NPPB*, and *NPR3* genes and the occurrence of ventricular dysfunction (VnD) after primary coronary artery bypass graft surgery.[1] We agree that assessing natriuretic peptide system gene SNPs for association with perioperative plasma B-type natriuretic peptide (BNP) levels may improve understanding of the underlying biology linking these SNPs to postoperative VnD, and we are currently conducting these analyses.

While we agree with Dr. Yu *et al.* that the association between natriuretic peptide SNPs and perioperative BNP concentrations should be assessed, the biological mechanisms for the association between these SNPs and postoperative VnD may be more complex than the pathway that they propose, ie. that natriuretic peptide system gene variants predict perioperative plasma BNP levels, which in turn predict postoperative VnD. As Dr. Yu and colleagues rightly point out, elevated plasma BNP is an established biomarker for heart failure.

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Indeed, we have previously reported that postoperative plasma BNP is significantly *increased* in patients who *develop* in-hospital VnD after coronary artery bypass graft surgery versus those who do not.[2] Despite the fact that circulating plasma BNP is known to be elevated in heart failure, we are aware of at least four studies of outpatient, non-cardiac cohorts that report that one or more of the *NPPA/NPPB* SNP alleles that we found associated with *decreased* VnD associate with *increased* plasma BNP levels (~10 pg/mL increase in plasma BNP for each copy of the minor allele).[3-6] One hypothesis to explain the seeming conundrum of why plasma BNP may be modestly elevated in ambulatory patients who carry *NPPA/NPPB* SNP alleles that are associated with decreased VnD may be that these SNPs code for *qualitative* as well as *quantitative* changes in circulating BNP. Indeed, recent studies have shown that there is functional heterogeneity in circulating forms of plasma BNP, with heart failure patients tending to have higher plasma ratios of biologically inactive precursor pro-BNP compared to subjects without heart failure.[7,8] Certain natriuretic peptide SNPs may be associated with increased production of biologically inactive BNP. Furthermore, there is evidence that natriuretic peptides have both autocrine and paracrine influences on ventricular myocardium.[9] Thus we can postulate that even though a natriuretic peptide gene SNP may associate with increased BNP levels, the qualitative nature of the BNP produced may mitigate the development of postoperative VnD through its direct effects on the myocardium.

In summary, we appreciate the comments of Dr. Yu and colleagues and fully agree that further study of natriuretic peptide system genes, circulating natriuretic peptides and natriuretic peptide tissue effects are needed in order to tease out mechanisms for our observed associations between *NPPA/NPPB* and *NPR3* gene variants and development of VnD after coronary artery bypass graft surgery.

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