Published in final edited form as:
J Cardiovasc Pharmacol. 2008 December ; 52(6): 500–506. doi:10.1097/FJC.0b013e31818f5739.

The β2 Adrenergic Receptor Gln27Glu Polymorphism Affects Insulin Resistance in Patients with Heart Failure:

Possible Modulation by Choice of Beta Blocker

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Abstract

Insulin resistance is prevalent in heart failure (HF) patients, and beta$_2$ adrenergic receptors (β_2-AR) are involved in glucose homeostasis. We hypothesized that β_2-AR Gln27Glu and Arg16Gly polymorphisms affect insulin resistance in HF patients and explored if effects of β_2-AR polymorphisms on glucose handling are modified by choice of beta blocker.

We studied 30 non-diabetic adults with HF and a history of systolic dysfunction, 15 on metoprolol succinate and 15 on carvedilol. We measured fasting glucose, insulin, and insulin resistance, and determined β_2-AR genotypes at codons 27 and 16. The cohort was insulin resistant with a mean HOMA-IR score of 3.4 (95%CI 2.3-4.5, normal value=1.0). Patients with the Glu27Glu genotype exhibited higher insulin and HOMA-IR compared to individuals carrying a Gln allele (p=0.019). Patients taking carvedilol demonstrated lower insulin resistance if also carrying a wild type allele at codon 27 (fasting insulin 9.8±10.5 versus 20.5±2.1 for variant, p=0.072, HOMA-IR 2.4±2.7 versus 5.1±0.6, p=0.074, respectively); those on metoprolol succinate had high insulin resistance irrespective of genotype. The β_2-AR Glu27Glu genotype may be associated with higher insulin concentrations and insulin resistance in patients with HF. Future studies are needed to confirm whether treatment with carvedilol may be associated with decreased insulin and insulin resistance in β_2-AR codon 27 Gln carriers.

Keywords

Heart failure; insulin resistance; receptors; adrenergic; beta; genetic polymorphism

INTRODUCTION

Heart failure (HF) leads to alterations in the metabolic pathways involved in glucose metabolism and insulin resistance, and these have been associated with worse outcomes.

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DISCLOSURES
The authors have no disclosures to declare.

[1-3] Diabetes mellitus is present in 20-25% of patients with chronic HF in large trials[4-6], and abnormal glucose metabolism and insulin resistance have been shown to be independent predictors of incident HF,[7-9] HF severity,[10] and HF mortality.[3] The exact mechanisms of insulin resistance in HF are unknown, although neurohormonal activation, particularly of the adrenergic system, is thought to play a role. Norepinephrine stimulates hepatic glucose production and affects glucose metabolism in part via the β_2 adrenergic receptor (β_2-AR). [11,12] It also increases lipolysis in adipose tissue leading to elevated levels of free fatty acids. [13] In patients with HF, insulin mediated decreases in plasma free fatty acids are attenuated compared to individuals without HF.[14]

Another potential factor altering glucose handling is genetic variation within the β_2-AR. Known single nucleotide polymorphisms (SNPs) in the β_2-AR gene include amino acid substitutions at codons 16 (Arginine [Arg] or Glycine [Gly]), and 27 (Glutamine [Gln] or Glutamic acid [Glu]). These 2 SNPs are highly prevalent (Gln27Glu: approximately 43% in Caucasians, 27% in Blacks; Arg16Gly: 39% Caucasians, 50% in Blacks), and have known effects on receptor function.[15] Several studies in patients with insulin resistance, diabetes, and obesity have demonstrated elevated post-load plasma glucose and fasting insulin concentrations in patients homozygous for the variant allele at either the Arg16Gly or Gln27Glu codon.[16,17] In healthy volunteers, the Gly16/Glu27 genotype has been associated with enhanced hepatic glucose production.[18]

Use of metoprolol succinate or carvedilol, both β-AR antagonists, is standard in the management of systolic dysfunction HF. While some studies indicate that beta blockers can worsen glycemic control,[19,20] metoprolol succinate and carvedilol have different adrenergic receptor pharmacology. Metoprolol's effect to worsen insulin resistance may be due to its β_1 selectivity,[19] while carvedilol has the potential to improve insulin sensitivity due to its β receptor non-selectivity and α_1 blockade.[19] A post-hoc analysis of the Carvedilol or Metoprolol European Trial (COMET) study demonstrated that new onset diabetes was more common in HF patients randomized to metoprolol tartrate than in those randomized to carvedilol.[21] It is therefore of interest to evaluate genetic factors influencing insulin resistance in HF patients, within the context of beta blockade with both metoprolol succinate and carvedilol at clinically relevant doses. We hypothesized that β_2-AR polymorphisms influence insulin resistance in patients with HF on β blockers. As an exploratory aim, we also hypothesized that the influence of β_2-AR polymorphisms on glucose handling can be modified by choice of beta blocker.

METHODS

Participants

We studied 30 non-randomized patients on target or maximally tolerated doses of β blocker therapy (15 metoprolol succinate and 15 carvedilol). Choice of β blocker was at the discretion of the treating clinician. Eligibility criteria included a history of systolic dysfunction (current or previous ejection fraction < 40%), with ACC/AHA Stage C, NYHA Functional Class II or III heart failure. All patients were on stable optimal medical therapy for heart failure for at least 30 days. Exclusion criteria included contra-indications to β-blockers; or concomitant use of scheduled inhaled β-agonists. In addition, patients with a prior diagnosis of diabetes mellitus, unstable angina, myocardial infarction or bypass surgery within the past 3 months, or underlying hypertrophic or restrictive cardiomyopathy were excluded. The protocol was approved by the University of Wisconsin institutional review board. All patients provided written informed consent in accordance with established guidelines for the protection of human subjects.

Study Protocol

This was a prospective cohort study in 30 individuals with a history of systolic dysfunction HF on guideline-based therapy, titrated to target (metoprolol succinate 200mg per day or carvedilol 25mg twice daily) or maximally tolerated beta blocker doses in the University of Wisconsin Hospital Heart Failure Management Program. The primary outcome variable was differences in fasting glucose and insulin concentrations, analyzed by genotype and by beta blocker therapy. Once patients gave informed consent, each had a fasting blood sample obtained by direct venipuncture for baseline glucose, insulin, and genotype analysis.

β_2-AR genotyping

Genomic DNA was extracted from 10 mL of whole blood with a DNA isolation kit (DNA Wizard, Promega, Madison, WI) following the manufacturer's suggested protocol. To determine genotype, polymerase chain reaction (PCR) was used to amplify the 250 base pair DNA region containing the β_2-AR polymorphisms at positions 27 and 16 for pyrosequencing. Reaction Primers (Integrated DNA Technologies, Coralville, IA) were designed using Primer3 software; forward primer 5′-TACACCACAGCCGCTGAAT-3′ and reverse primer 5′-GGACGATGAGAGACATGACG-3′. PCR amplification was carried out in a volume of 37.5 μL containing 100 ng DNA, 5 pmol of each primer, and PCR master mix containing 1.0 U Taq DNA polymerase, 1.5 mM $MgCl_2$, and 0.2 mM of each deoxynucleoside triphosphates (Promega, Madison, WI). The reactions were incubated at 94°C for 6 minutes, followed by 35 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 60 seconds, with a final extension of 72°C for 5 minutes. Amplification was verified by electrophoresis on a 2% agarose gel and stained with ethidium bromide. PCR products were stored in a -70°C freezer until pyrosequencing reactions commenced after enrollment of the entire cohort. The pyrosequencing PSQ 96MA system (Biotage, Foxboro, MA) and the forward sequencing primer 5′-TTGCTGGCACCCAAT-3′ were used to determine genotypes.

Data Analyses

Baseline demographics, including characteristics by genotype, were compared to identify potential differences between groups using t-tests or Wilcoxon rank sum tests for continuous variables and Chi-Square or Fisher's exact tests, as appropriate, for categorical variables. Hardy-Weinberg equilibrium was assessed by the Chi-Square test. Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR): fasting values of glucose (mmol/L) x insulin (μIU/mL) / 22.5.[22]

The primary study outcome variable for statistical analysis was mean fasting glucose and insulin levels at baseline. Assuming a 20% difference in fasting glucose and insulin concentrations (standard deviation = 15%[16]) by genotype, 30 subjects were needed to achieve 80% power at the 0.05 significance level based on published population genotype frequencies.[15] Power to detect differences in analyses stratified by β-blocker was 54%, assuming a 15% difference in fasting glucose and insulin by β blocker. It was determined *a priori* to compare participants with the homozygous variant genotype to heterozygous and wild type genotypes, as homozyogous individuals have been shown in previous studies to have worse cardiovascular and metabolic outcomes. Insulin, insulin resistance (HOMA-IR score), and glucose levels between homozygous variant and heterozygous participants for codons 27 and 16 were compared using the Wilcoxon rank sum test. Multivariable linear regression models were created to examine associations between genotype (homozygous variant vs. wild type carriers) and insulin and glucose measures while adjusting for specific beta-blocker treatment. Log-transformations of the outcome measures were performed where necessary. Separate models were created for each outcome variable (insulin, HOMA-IR score, and glucose levels) and for each codon (27 and 16). Each model was adjusted for body mass index (BMI as a continuous variable), and HF etiology (ischemic versus idiopathic). A genotype/beta-

blocker interaction term was entered into the final multivariable model. P-values of <0.05 were considered significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Patients

Thirty patients (9 females, 21 males) were enrolled, with a mean age of 57.8 ± 15.0 years (range 27-81 years). Mean ejection fraction was 34.6% ± 10.1% (range 15%-55%), and most were NYHA functional class II. Demographics, phenotypic and genotypic characteristics are shown in Tables 1 and 2. Arg16Gly and Gln27Glu frequencies in the sample were in Hardy-Weinberg equilibrium. No statistically significant demographic differences were observed at baseline between the beta blocker groups. For Arg16Gly, more males carried the homozygous genotype (Gly16Gly, p=0.018). Mean fasting glucose concentration in the sample was 101.5 mg/dL (95% CI 97.1-105.9), and mean insulin concentration was 13.1 μIU/mL (95% CI 9.2-17.0, normal range 3-19 μIU/mL). Mean HOMA-IR score was 3.4 (95% CI 2.3-4.5, normal value = 1.0), indicating a high prevalence of insulin resistance in the cohort.

Levels of fasting glucose, insulin, and insulin resistance by β2 polymorphisms

No significant differences in fasting glucose were detected between patients homozygous (n=9) for the variant Glu allele at codon 27 versus the 21 patients carrying at least one wild type Gln allele, (107.4 ± 13.4 mg/dL for Glu27Glu compared with 99.0 ± 10.4 mg/dL for Gln carriers, p=0.15). Nevertheless, homozygous variant patients had higher fasting insulin concentrations than those carrying at least one wild type allele (17.4 ± 6.8 μIU/mL versus 11.2 ± 11.4 μIU/mL, p=0.019). Similarly, HOMA-IR scores were higher for patients homozygous variant compared to wild type allele carriers at codon 27 (4.7 ± 2.0 versus 2.9 ± 3.2, p=0.019). (Figures 1 and 2) There were no differences in glucose, insulin or HOMA-IR levels between of genotype groups at codon 16.

Levels of fasting glucose, insulin, and insulin resistance by beta-blocker

There were no statistically significant differences detected between the carvedilol and metoprolol succinate groups in fasting glucose (100.1 ± 8.7 mg/dL versus 102.9 ± 14.4 mg/dL,p=0.63) insulin (11.2 ± 10.4 μIU/mL versus 15.0 ± 10.7 μIU/mL, p=0.20), and HOMA-IR scores (2.8 ± 2.7 versus 4.0 ± 3.2, p=0.19).

Levels of fasting insulin and insulin resistance by β2 polymorphisms within beta blocker treatment subgroups

Results for fasting insulin and HOMA-IR were examined by genotype at codon 27 within beta blocker therapy subgroups. Patients on carvedilol, but not those on metoprolol succinate, had lower mean insulin and HOMA-IR values when carrying a wild type allele at codon 27 (Figures 3 and 4), a result short of statistical significance (fasting insulin 20.5 ± 2.1 versus 9.8 ± 10.5, p=0.072, and HOMA-IR 5.1 ± 0.6 versus 2.4 ± 2.7, p=0.074, respectively).

Multivariable models

Multivariable linear models were created for each outcome variable (insulin, HOMA-IR, and glucose) to determine if a genotype by beta blocker interaction was present after adjustment for BMI, NYHA FC, and etiology. Separate models were created for each of the 3 outcomes, and each SNP (Arg16Gly and Gln27Glu). No significant interactions were detected in any of the beta blocker models. As expected, BMI was a significant predictor of insulin levels and HOMA-IR in both codon 16 and codon 27 models (p=0.003). Ischemic etiology was a significant predictor of higher insulin levels in both SNP models (p=0.037).

DISCUSSION

Our results show that polymorphisms in codon 27 of the β_2-AR may be associated with serum insulin levels and insulin resistance; moreover, the data suggest that choice of β-blocker may modify the relationship between β_2-AR genotype and insulin resistance. In light of the high incidence of diabetes and insulin resistance in patients with HF, and that treatment with beta blockers may increase the risk of diabetes, the relationship between genetic predisposition to insulin resistance and beta blocker choice may have important clinical implications in HF patients.

Heart failure and diabetes are related in a complex and incompletely understood fashion. The incidence of new diabetes in patients with HF is very high, ranging from 2-7% per year as compared with 0.1-0.4% in hypertensive populations.[21,23-25] The HF patients in our cohort had markedly elevated insulin resistance, consistent with previous study findings.[2] We demonstrate that patients homozygous for the glutamate variant (Glu27Glu) at codon 27 of the β_2-AR had higher fasting insulin concentrations and insulin resistance than patients carrying a wild type allele. The adrenergic system controls glucose metabolism in the liver, adipose tissues, and skeletal muscle, partially through β_2-AR.[26] In addition to effects on glucose metabolism, the β_2-AR has increased importance in HF. In normal hearts, the β_1 receptor predominates, with a β1:β2 ratio of approximately 80:20. In HF, β_1 receptors downregulate, decreasing the β1:β2 ratio to 60:40.[27,28] It is logical then to theorize that β_2-AR metabolic effects may have more importance in HF. Two non-synonymous single nucleotide polymorphisms (SNPs) at nucleotides 46 and 79 of the β_2-AR gene result in changes in amino acid residues 16 (Arginine [Arg] or Glycine [Gly]), and 27 (Glutamine [Gln] or Glutamic acid [Glu]).[15,29] The variant genotypes are resistant to agonist-induced receptor downregulation, whereas the wild type carriers have preserved downregulation.

Given their high prevalence, functional consequences, and the known physiologic links of adrenergic pathways to endocrine function, it is not surprising that the Gln27Glu polymorphism may be related to insulin resistance in HF patients. In a study of the effect of β_2-AR haplotypes on terbutaline-mediated glucose production and insulin concentrations in healthy volunteers, [18] participants carrying the Glu27 homozygous genotype had more pronounced terbutaline-mediated glucose production and, similar to our findings, higher insulin concentrations compared with participants with a Gln27 allele. Similarly, in a study of 155 healthy individuals [30] the β_2-AR Arg16Gly variant, specifically the Gly16 allele, was associated with increased insulin resistance. We did not find any association between the Arg16Gly SNP and insulin resistance. Haplotype analyses would be desirable for future studies as the β_2-AR Arg16Gly and Gln27Glu variants are in tight linkage disequilibrium. As our study was exploratory, it was not designed to perform haplotype analyses. Interestingly, it is not uncommon to observe one SNP driving the biologic effect even in studies that include haplotype analyses. Our data would suggest that the Gln27Glu variant has primary importance in regulation of insulin resistance in HF. Future work should address the issue of β_2-AR haplotypes more specifically. [15]

Additionally, we observed a trend for an association between β_2-AR genotype at codon 27 and choice of β blocker on fasting insulin and insulin resistance, although our results were short of statistical significance. In patients prescribed carvedilol who had a wild type Gln allele at codon 27 insulin resistance was lower. Patients treated with metoprolol succinate irrespective of genotype at codon 27 and those homozygous for the variant allele treated with carvedilol all demonstrated higher insulin resistance. Although these results are intriguing, they should be considered exploratory, requiring confirmation in larger cohorts with power to test interactions of genotype with beta blocker treatment on metabolic outcomes. To our knowledge, this study is the first to examine a genotype by beta blocker interaction on metabolic outcomes in HF.

The mechanisms by which different beta blockers might affect insulin resistance in Glu27Glu patients remain unclear. Carvedilol is a non-specific adrenergic blocker at all doses, with blockade of β_1, β_2 and α_1 receptors, while metoprolol succinate is β_1 selective at lower doses and β_1/ β_2 nonselective at higher doses. The relative increase in importance of β_2-AR specifically in HF and the role of the β_2AR in glucose metabolism may provide a clue regarding the specificity of carvedilol to reduce insulin resistance by β_2AR genotype. Glucose uptake is dependent on adequate blood flow, determined by both α_1 and β_2-AR tone. Blockade of β_2-AR would potentially decrease peripheral blood flow, especially in the setting of unopposed α_1 stimulation. Blockade of α_1 receptors may lead to increased peripheral glucose utilization; [31] we did not directly examine α_1 effects in this study. The relative importance of α and β-adrenergic receptors in mediating catecholamine-induced hepatic glucose handling is yet to be resolved. [26] It is possible that individuals carrying the variant Glu27Glu genotype treated with carvedilol have more pronounced β_2-AR blockade, hence changing relative β_1: β_2: α_1 effects, altering the balance of peripheral vasoconstriction and glucose uptake compared to the wild type Gln carriers.

Other investigators explored associations of β_2-AR variants on the risk of sudden cardiac death in an older adult cohort, on mortality in individuals following an acute coronary syndrome, and on the risk of death and heart transplantation in patients with heart failure.[32-34] Elevated cardiovascular risk was associated with the Gln27Gln and Arg16Arg genotypes. In contrast, we detected higher insulin concentrations and insulin resistance in the Glu27Glu genotype, presumably correlating with negative cardiovascular outcomes. Differing outcome measures, study sample characteristics and cohort sizes, or additional genetic factors could all contribute to these discordant results. β_1-AR variants have also been studied for associations with adverse cardiac risks in addition to interactions with beta blocker efficacy based on genotype.[35,36]

Although we found differences in insulin concentrations and insulin resistance based on β_2-AR genotype in this study, we did not see differences in fasting glucose concentrations. This is not necessarily unexpected, as early in the insulin resistance syndrome post-prandial glucose levels are affected while fasting glucose, measured in this study, is unchanged. Similarly, in the COMET study, there were no significant differences in blood glucose concentrations between carvedilol and metoprolol tartrate, despite a 20% higher incidence of new onset diabetes in the metoprolol treatment arm over the course of the trial.[21] The GEMINI study examining metabolic variables in patients with diabetes assigned to carvedilol or metoprolol, found similar mean blood glucose concentrations between the two agents over a follow up course of 5 months, yet higher HbA1c values in the metoprolol group.[20] We did not note significant differences between carvedilol and metoprolol succinate in fasting glucose, insulin, and HOMA-IR, but were not powered to detect them, and therefore recommend that future studies continue to examine potential differences.

A number of limitations should be noted. It is conceivable that selection bias influenced subject treatment with the different beta blockers, favoring including patients carrying a genotype that affords improved tolerability to target beta blocker doses studied. In prior studies, differences in beta blocker tolerability based on β_2-AR polymorphisms have not been found.[37] We did not have baseline metabolic and body mass index data prior to beta blocker initiation. We therefore attempted to capture chronic metabolic changes from beta blocker therapy in patients with target or maximally tolerated beta blocker doses, which we thought is clinically relevant. This was a nonrandomized study, and as such, the clinician's choice of beta blocker could have been influenced by his/her impression of their differing metabolic effects, which could have affected comparisons made between β blockers. It is also possible that higher number of patients who were NYHA functional class III in the metoprolol group compared to the carvedilol group could have affected the genotype by β blocker trends we observed on metabolic outcomes. However, mean ejection fractions were not significantly different

between beta blocker groups. We did not account for the influence of ejection fraction on our outcomes, which could have influenced study results. The generalizability of our results to a wider group of patients, especially those with more advanced HF, is unknown. We cannot rule out that our findings among Gln27 carriers taking carvedilol are due to chance based on our small sample size, limited power to examine an interaction of genotype on beta-blocker effects, and negative beta blocker by genotype interaction term in our multivariable models. However, we felt beta blocker effect on insulin sensitivity was a secondary endpoint worthy of exploration. Due to issues of sample size, it was not feasible in this cohort to study β_2-AR haplotypes at positions 16 and 27. This cohort study should not be used to infer causality but demonstrates an association between a common β_2-AR polymorphism and insulin resistance which may be associated with specific choice of beta blocker therapy in HF patients. We do not currently support beta blocker choice determination based on β_2-AR genotype based on this pilot study.

CONCLUSIONS

The β_2-AR Glu27Glu genotype is associated with higher insulin concentrations and worse insulin resistance in patients with HF. Our data suggest that decreased insulin resistance in β_2-AR codon 27 Gln carriers may be associated with treatment with carvedilol. Future studies should examine interactions of β_2-AR genotype and beta blockers on glucose dynamics in heart failure.

ACKNOWLEDGMENTS

We gratefully acknowledge Drs. Walter Kao, David Murray, Peter Rahko, and Elaine Winkel for allowing their patients to participate in this study.

FUNDING SOURCES

Dr. Vardeny was supported by NIH (NCRR) 8K12RRO23268 and the American Association of Colleges of Pharmacy. Dr. Sweitzer was supported by NIH K23AG01022.

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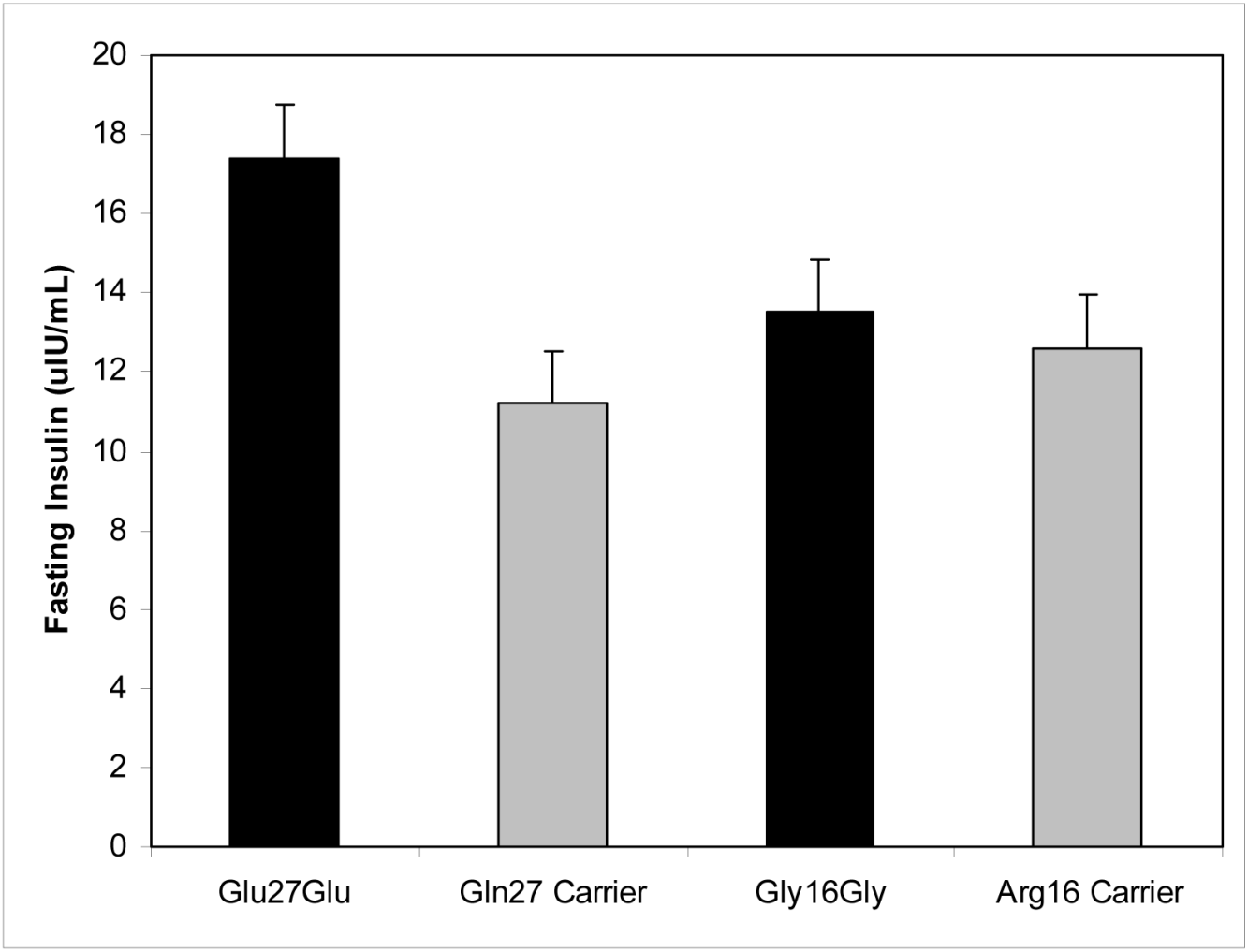

Figure 1.
Fasting insulin stratified by β_2-AR genotype at codons 27 and 16 (homozygous variant versus wild type carrier). Data are means ± SE. * **p=0.019** for comparison between Glu27Glu and Gln carriers. P=NS for comparison of Arg16Gly genotypes.

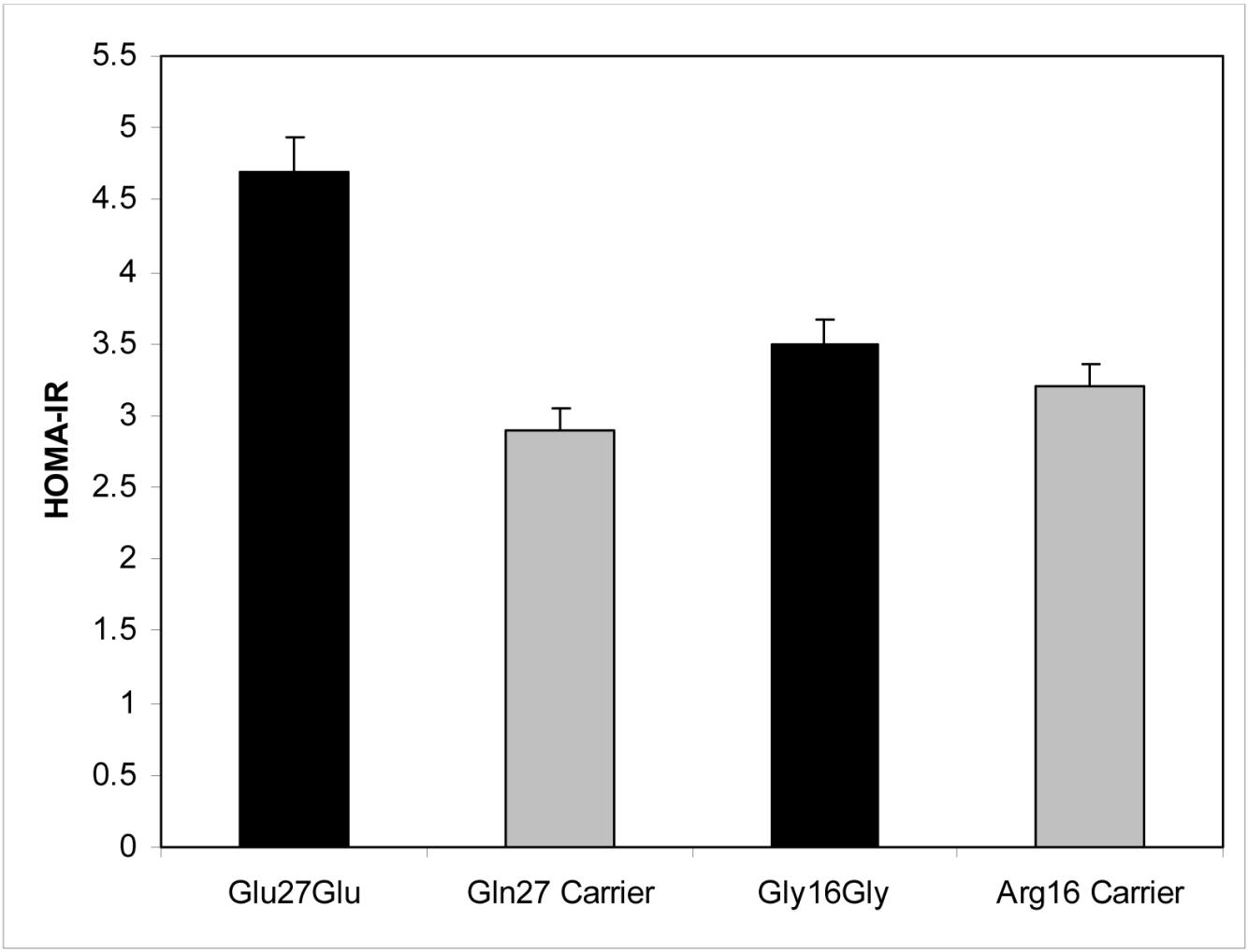

Figure 2.
HOMA-IR stratified by β_2-AR genotype at codons 27 and 16 (homozygous variant versus wild type carrier). Data are means ± SE. * **p=0.019** for comparison between Glu27Glu and Gln carriers. P=NS for comparison of Arg16Gly genotypes.

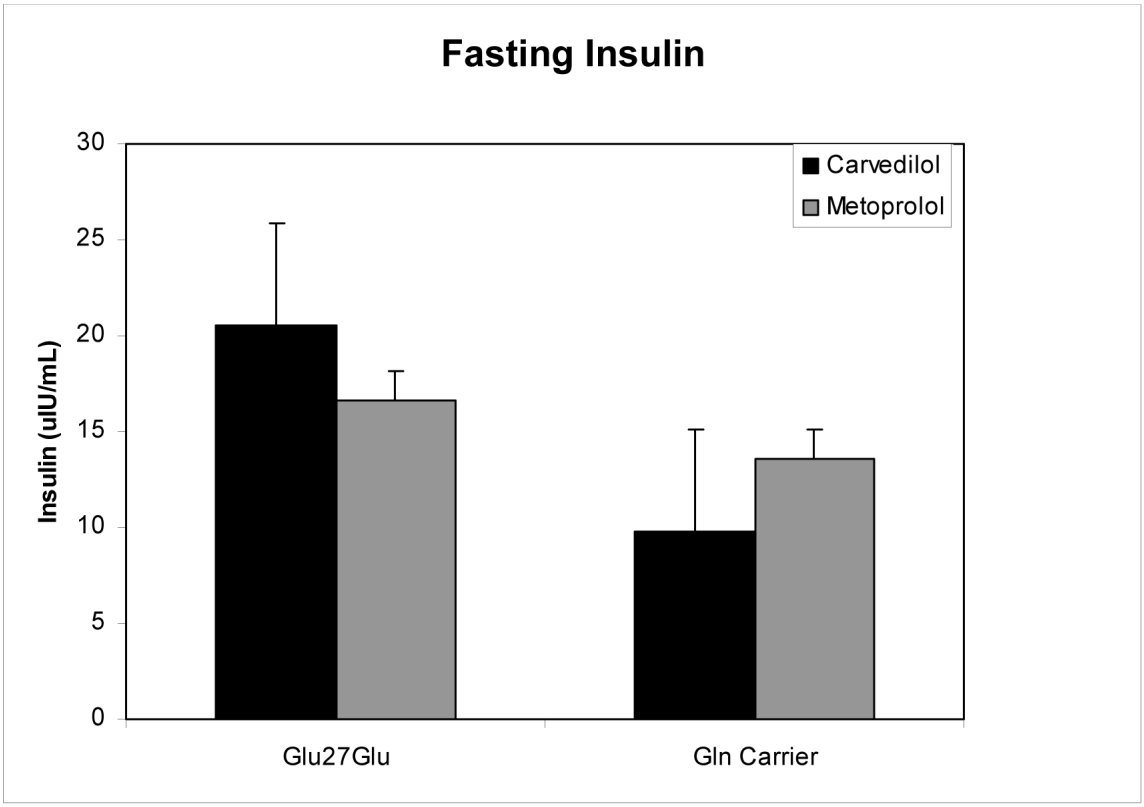

Figure 3.
Fasting insulin stratified by β_2-AR Gln27Glu genotype and by beta blocker (carvedilol versus metoprolol). Data are means ± SE. * **p=0.072** for comparison of Glu27Glu genotype to Gln carrier in the carvedilol cohort.

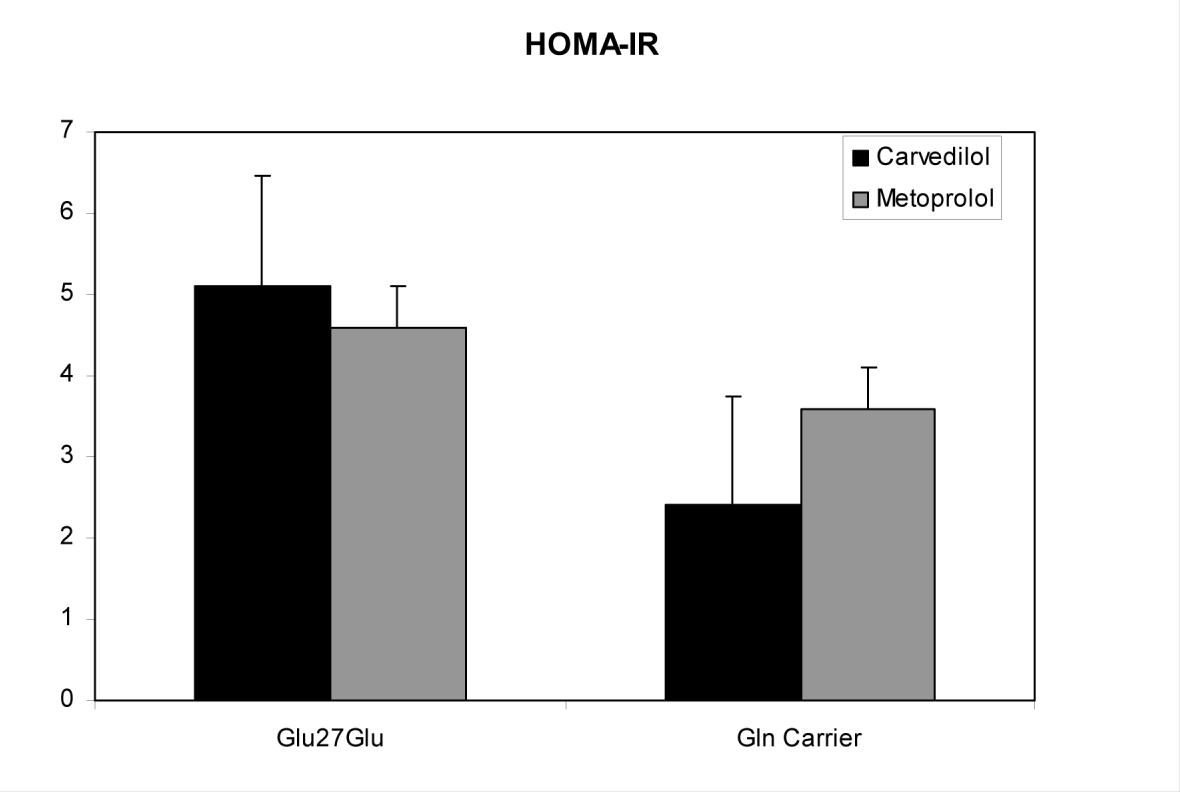

Figure 4.
HOMA-IR stratified by β_2-AR Gln27Glu genotype and by beta blocker (carvedilol versus metoprolol). Data are means ± SE. * **p=0.074** for comparison of Glu27Glu genotype to Gln carrier in the carvedilol cohort.

Table 1

Baseline demographics, Total and by beta blocker

Variable	All Subjects (N=30)	Carvedilol (N=15)	Metoprolol (N=15)	P carvedilol vs. metoprolol
Age (yrs)	57.8 ± 15.0	54.8 ± 17.8	60.9 ± 11.3	0.38
Men, n (%)	21 (70)	10 (67)	11 (73)	1.00
White/black/Hispanic	27 /1 / 2	14/0/1	13/1/1	0.89
NYHA FC II/III	27 (90%) / 3 (10%)	15(100 %) / 0(0%)	12(80%) / 3(20%)	0.22
Ischemic heart disease	11 (37%)	5 (33%)	6 (40%)	0.70
Body mass index	30.1 ± 5.1	29.6 ± 5.5	30.6 ± 4.9	0.46
LVEF* (%), range	34.6% ± 10.1%, 15-55%	34.7 ± 10.1, 15-55%	34.6 ± 10.6, 15-55%	0.93
Background therapy				
ACE inhibitor / ARB**	29 (96.7%)	15 (100%)	14 (93%)	1.0
Furosemide	21 (70%)	11 (73%)	10 (67%)	0.99
Digoxin	15 (50%)	9 (60%)	6 (40%)	0.27
Spironolactone	12 (40%)	6 (40%)	6 (40%)	1.00
Statin	22 (73%)	11 (73%)	11 (73%)	1.00

* LVEF: left ventricular ejection fraction

** ARB: angiotensin receptor blocker

Table 2

Baseline demographic characteristics, stratified by β2-AR genotype(homozygous variant versus wild type carriers)

Variable	Glu27Glu (N=9)	Gln27 carriers (N=21)	Gly16Gly (N=17)	Arg16 carriers (N=13)
Age (yrs)	57.3 ± 12.7	58.0 ± 16.1	55.7 ± 15.4	60.6 ± 14.5
Men	7 (78%)	14 (67%)	15 (88%)†	6 (46%)
White/black/Hispanic	8 / 1 / 0	19 / 0 / 2	16 / 1 / 0	11 / 0 / 2
NYHA FC II/III	9 / 0	18 / 3	15 / 2	12 / 1
Ischemic heart disease	4 (44%)	7 (33%)	8 (47%)	3 (23%)
Body mass index	32.2 ± 4.2	29.1 ± 5.3	29.6 ± 5.3	30.7 ± 4.9
LVEF (%)	40.0% ± 10.0%	32.3% ± 9.5%	34.1% ± 11.6%	35.3% ± 8.2%
Background therapy				
Beta blocker (C or M#)	4 / 5	11 / 10	7 / 10	8 / 5
ACE inhibitor / ARB	8 / 1	19 / 2	16 / 1	11 / 2
Furosemide	5 (56%)	16 (76%)	10 (59%)	11 (85%)
Digoxin	2 (22%)	13 (62%)	7 (41%)	8 (62%)
Spironolactone	4 (44%)	8 (38%)	6 (35%)	6 (46%)
Statin	5 (56%)	17 (81%)	12 (71%)	10 (77%)

*Data are mean ± SD

#C = carvedilol; M = metoprolol succinate

†P=0.018 for sex comparing Gly16Gly and Arg16 carriers