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A Combination of Low Doses of Fluvastatin and Valsartan Decreases Arterial Stiffness in Patients After Myocardial Infarction: A Pilot Study

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ABSTRACT

Background: Despite optimum treatment, patients who experience myocardial infarction are still at high risk for future events.
Objective: We evaluated the effect of 30 days of treatment with combination of low, subtherapeutic doses of fluvastatin and valsartan on arterial stiffness in patients after myocardial infarction, a therapy that has not been used yet.
Methods: Fourteen male patients with a history of myocardial infarction were enrolled into a pilot double-blind randomized controlled study. They were allocated to receive 10 mg fluvastatin and 20 mg valsartan or placebo for 30 days in addition to their regular pharmacotherapy. Carotid–femoral pulse wave velocity was measured on inclusion, after 30 days, and after 3 months.
Results: Mean (SD) carotid–femoral pulse wave velocity decreased significantly in the treatment group after 30 days and persisted at lower values after 3 months (from 8.4 [1.5] m/sec to 7.3 [1.1] m/sec to 7.2 [0.8] m/sec; $P < 0.05$). The 95% CI for decrease after 30 days in the treatment group was 0.5–1.6. Only nonsignificant changes were observed in the control group. Serum lipid levels and arterial blood pressure did not change significantly in any group.
Conclusions: The treatment resulted in a significant and sustained improvement of arterial stiffness in male patients with a history of myocardial infarction, which highlights the need for further study of this new approach.

Introduction

Patients with a history of myocardial infarction (MI) are at higher risk for future major adverse cardiovascular events.[1] This risk can be decreased using established pharmacologic and nonpharmacologic interventions aiming to reduce traditional risk factors.[2] However, the risk remains elevated compared with the general population.[1] This highlights the need for developing new strategies of secondary prevention. Arterial stiffness, expressed as carotid–femoral pulse wave velocity (cfPWV), was identified as an independent prognostic indicator of future major adverse cardiovascular events in patients experiencing MI.[3,4]

We therefore performed a pilot study to evaluate the effect of a combination of low doses of fluvastatin and valsartan (low-flu/val) on arterial stiffness in men with a history of MI who are already receiving optimal pharmacologic and nonpharmacologic treatment.

Patients and Methods

We performed a double-blind randomized placebo-controlled pilot study on male post-MI patients. The study design was approved by the National Medical Ethics Committee of Slovenia. All subjects provided written informed consent before inclusion.

The patients were recruited from the participants of the cardiac rehabilitation program at the University Medical Centre in Ljubljana. The inclusion criteria were male sex; age >55 years; >6 months and <5 years after MI; infarction resolved with primary percutaneous coronary intervention with stenting; and receiving optimal pharmacologic and nonpharmacologic treatment according to current guidelines. All patients were treated with antiplatelet agents (ie, aspirin), statins (ie, atorvastatin or rosuvastatin), angiotensin converting enzyme inhibitors (ie, perindopril or

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ramipril), or angiotensin receptor blockers (ie, candesartan) and β-blockers (ie, bisoprolol), according to Slovenian and European guidelines. Patients with chronic diseases, diabetes, and those receiving fluvastatin or valsartan were excluded.

Patients were randomized to 2 groups using a simple balanced algorithm (computer-generated random numbers). Treatment substances were in the form of tablets, identical to one another, packed in opaque white containers. The key to resolving the content of each numbered container was stored by the pharmacist. The allocation sequence obtained was concealed from the researchers enrolling and assessing participants by being placed in a sealed envelope. The treatment group received 10 mg fluvastatin and 20 mg valsartan (Novartis, Basel, Switzerland) once daily for 30 days, whereas the control group received placebo.

We performed 3 measurements: on inclusion, after 30 days, and after 3 months. On every visit each patient's blood pressure was measured and they were briefly examined and questioned on their current weight, possible side effects of treatment, compliance with their regular therapy, and the study protocol. Fasting venous blood samples were obtained during every visit. Cholesterol and triglyceride levels were measured in blood serum using the VITROS 5,1FS Chemistry System (Ortho Clinical Diagnosis, Inc, Raritan, NJ), a validated method and laboratory system. The values of LDL cholesterol were calculated using the Friedewald equation. Measurements of cfPWV were then performed using SphygmoCor device (AtCor Medical, Sydney, Australia) with SphygmoCor CvMS software (version 9). The measurements were performed as previously described elsewhere[5] and in accordance with the latest Expert Consensus Document.[6] Because the study was based on repeated measurements, the difference between the distance from the jugular notch to the measuring site on the femoral artery and the distance between the measuring site on the carotid artery and the jugular notch were used to calculate pulse wave velocity (PWV).

All values were expressed as mean (SD). For an 80% chance of detecting a 1 m/sec decrease in cfPWV using mixed ANOVA for repeated measures, 6 patients would be needed in each group, assuming a mean cfPWV of 8.2 (0.5) m/sec and correlation coefficient between repeated measures of 0.5. These assumptions were based on our previous unpublished measurements on a group of post-MI patients.

Patient characteristics on inclusion were compared using 2-tailed *t* tests for independent samples assuming equal variances or Fisher's exact test. We used mixed ANOVA for repeated measures to compare cfPWV values measured on every visit—with time as the within-patient factor and treatment as the between-patients factor. A P value < 0.05 was considered significant. All statistical analyses were performed using SPSS version 20.0 (IBM-SPSS Inc, Armonk, NY).

Results

We included 14 patients in the study. There were no statistically significant differences between the 2 groups (Table). None of the patients reported any side effects that could be attributed to low-flu/val. Serum lipid levels, systolic blood pressure, and diastolic arterial blood pressure did not change significantly during the study.

On inclusion, cfPWV did not differ significantly between the groups (treatment = 8.4 [1.5] m/sec and control = 8.0 [0.2] m/sec; $P = 0.521$). During the study the mean cfPWV decreased significantly in the treatment group after 30 days and persisted at lower values after 3 months (to 7.3 [1.1] m/sec in 30 days and 7.2 [0.8] m/sec in 3 months), whereas it fluctuated in the control group (F [2, 24] = 4.05; $P = 0.031$) (see the Figure). The 95% CI for decrease after 30 days in the treatment group was 0.5 to 1.6.

Table
Patients' characteristics on inclusion.

Variable*	Treatment group (n = 7)	Control group (n = 7)
Age, y	46.7 (6.4)	50.6 (2.7)
Body mass index, kg/m^2	30.9 (3.5)	30.0 (4.9)
Time after MI, whole mo	19 (20)	25 (14)
Total cholesterol, mmol/L	4.13 (1.41)	4.01 (0.81)
LDL cholesterol, mmol/L	2.10 (0.65)	2.06 (0.73)
HDL cholesterol, mmol/L	1.07 (0.09)	1.18 (0.14)
Triglycerides, mmol/L	2.25 (2.45)	1.68 (0.62)
Systolic BP, mm Hg	118 (6)	124 (8)
Diastolic BP, mm Hg	80 (3)	79 (8)
Statins	6	7
ARBs	0	1
ACE inhibitors	5	5

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; MI = myocardial infarction.

*Numeric variables (age, body mass index, time after MI, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic BP, and diastolic BP) are expressed as mean (SD). Medication variables (statins, ARBs, and ACE inhibitors) are expressed as n. None of the differences between groups was statistically significant.

Discussion

In our pilot study, we aimed to evaluate the effect of 30-days of treatment with low-flu/val on arterial stiffness of male patients with a history of MI who were already receiving optimal treatment according to current guidelines, including inhibitors of the renin–angiotensin system and statins. Our intervention significantly reduced arterial stiffness, expressed as cfPWV, without significantly affecting serum lipid levels or arterial blood pressure. This effect persisted at a significant level even 2 months after discontinuation of treatment.

In patients with a history of MI, arterial stiffness was mainly investigated as a predictor of future major adverse cardiovascular events and not as a possible target for intervention; it has been clearly shown that arterial stiffness is a good prognostic factor. However, there is no prospective study that would estimate the clinical value of decreasing arterial stiffness by either pharmacologic or nonpharmacologic approaches. Drugs frequently used in post-MI patients, such as statins and drugs affecting the renin–angiotensin system, might to some degree decrease arterial stiffness. Importantly, this was shown for therapeutic doses of these drugs. Nevertheless, it seems logical that an additional decrease in

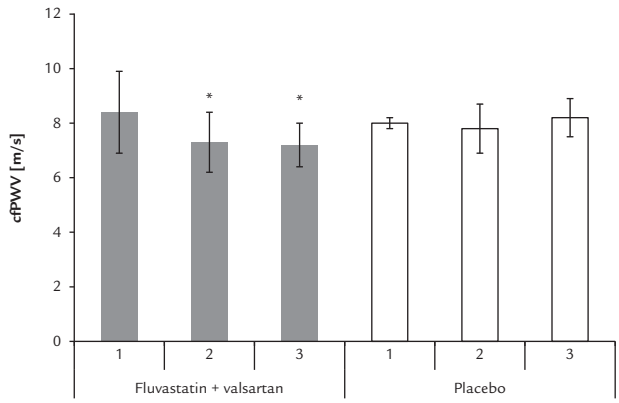

Figure. Mean carotid–femoral pulse wave velocity (cfPWV) (SD) during the study. 1 = on inclusion; 2 = after 30 days; 3 = after 3 months. *$P < 0.05$ in mixed ANOVA for repeated measures.

arterial stiffness would improve the prognosis of post-MI patients. However, such an approach is not known so far.

The effect of statins (at therapeutic dose) on arterial stiffness was studied by Jia et al.[7] They showed a beneficial effect on cfPWV of 40 mg/d simvastatin on top of other pharmacologic therapy (statins excluded) in patients treated immediately after MI for 6 months. The patients were not randomized but divided into hyper- and normocholesterolemic groups, based on baseline cholesterol levels. Both groups received the same treatment, but the decrease in arterial stiffness was greater in the hypercholesterolemic group. The effect of low therapeutic doses of statins on arterial stiffness in patients with stable coronary artery disease and hyperlipidemia was studied by Meng et al.[8] Patients who had not previously been treated with lipid-lowering drugs were consecutively allocated to receive 10 mg/d atorvastatin and a low-fat diet for 6 months or only a low-fat diet. cfPWV decreased significantly in the treatment group after 6 months, but the decrease measured after 3 months was nonsignificant. A randomized study in patients with hypertension and hyperlipidemia, using the same drug dosages as above, also demonstrated a significant decrease in cfPWV after 6 months.[9]

The combination of fluvastatin and valsartan has synergistic beneficial effects in vitro.[10,11] In 2 previous clinical studies performed in apparently healthy middle-aged male patients[12] and patients with type 1 diabetes,[13] our group showed that 30-day treatment with low-flu/val significantly lowered arterial stiffness.

A meta-analysis of studies using antihypertensive agents in patients with hypertension to lower arterial stiffness showed that the decrease in cfPWV was significantly larger in long-term (>4 weeks) than in short-term (<4 weeks) trials: 1.3 m/sec versus 0.75 m/sec.[14] The mean decrease of cfPWV after our 30-day intervention approached the decrease observed in long-term trials. Contrary to our study, the lowering of cfPWV in long and short-term trials paralleled a decrease in blood pressure. It was suggested that a decrease in arterial stiffness independent of blood pressure reduction could occur in long-term trials.[14] In our study, serum lipid levels remained unchanged, whereas even in studies in which low doses of statins (eg, atorvastatin 10 mg/d) were used[8,9] the reduction in stiffness was paralleled by a decrease in total cholesterol levels of 1.87 and 1.90 mmol/L, respectively. Serum cholesterol levels did not change significantly in the clinical study using low-flu/val.[12] However, a small effect in our study cannot be excluded because of inadequate power to detect it.

To our knowledge, low-flu/val has not yet been used to reduce arterial stiffness in post-MI patients already receiving all established pharmacologic therapy. Although other studies have shown that therapeutic doses of statins and angiotensin receptor blockers can improve arterial stiffness, we have, surprisingly, shown that the addition of low-flu/val gives an additional improvement of arterial stiffness. We assessed arterial stiffness using cfPWV, which is the gold standard in this field.[6] Our innovative approach has the advantages of producing a sizeable effect in a short period of time and using well-known drugs in low doses, thus minimizing the risk of unwanted side effects and poor compliance. It appears that the observed effect was independent of changes in serum lipid levels and arterial blood pressure. In addition, we observed the phenomenon of prolonged effect, because beneficial effects on arterial stiffness persisted even 2 months after treatment discontinuation. The same phenomenon has been continuously observed in all our studies performed on different populations.

Our pilot study was limited in the number of patients. Furthermore, the mechanism of action of low-flu/val administered on top of other drugs is at present unknown, although a previous study[15] has shown that a combination of low, subtherapeutic doses of statins and angiotensin receptor blockers influences the expression of vasoactive genes in rat aortas, which could also be the mechanism of action in humans. Overall, we believe that our encouraging pilot results, which possibly have clinical value, warrant further study.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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