Effects of lidocaine on membrane stabilization in harvested vein graft storage

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ABSTRACT

الأهداف: فحص الآثار لعقار ليدوساين على شكل الأوردة الصافنة (SVs) المأخوذة كعملية إجراء مجازة للشريان التاجي (CABG).

الطريقة: أجريت هذه الدراسة بجامعة غازي – قسم جراحة الأوعية الدموية – أنقرة – تركيا، خلال الفترة ما بين مايو 2007م وحتى سبتمبر 2007م. تم أخذ أوردة صافنة (SVs) من 11 مريض خضعوا لعملية تركيب مجازة للشريان التاجي (CABG)، وتم تقسيمهم إلى ثلاث أقسام. كل مجموعة من نفس موقع الترقيع وتم تقسيمها إلى ثلاث مجموعات: مجموعة التحكم (C)، والمجموعة التي تلقت المحلول الملحي الفسيولوجي (PS)، والمجموعة التي تلقت عقار ليدوساين (L). تم قياس مستويات سينثاس أكسيد النتريك (NOS)، وتجمع أكسيد النتريك، ودسموتيس الأكسيد العلوي (SOD) وتفاعل حمض ثيوباربوتريك (TBARS) في عينات من المجموعات. تم تقييم العينات النسيجية وفقاً للفئة المحددة مسبقاً والنقاط وفقاً لذلك.

النتائج: كانت نتيجة الفحص النسيجي للرقعات في المجموعة (L) والمجموعة (C) متشابهة، ولكن كانت النقاط النسيجية للرقعات في المجموعة (PS) أعلى من الناحية الإحصائية من المجموعة (p>0.05) (C). كان نشاط (NOS) وتجميع (NO) أعلى في المجموعة (L) والمجموعة (PS) من المجموعة (0.05p) (C). كان نشاط (SOD) أعلى في المجموعة (L) من المجموعة (PS 0.05p>). كان نشاط (SOD) أقل في المجموعة (PS) من المجموعة (0.05p) (C>). لم يكن هنالك فرقاً إحصائياً بين مستويات (TBARS) لجميع المجموعات.

خاتمة: تشير نتائجنا إلى أن التلف الأولي قد يظهر خلال العملية الجراحية نتيجة للإصابة أثناء أخذ الرقعة، وقد تظهر الإصابات الناجحة نتيجة لإصابة إعادة الانصباب لنقص التروية بالدم أثناء فترة الانتظار. يحمي عقار ليدوساين الإصابة المتأخرة بإضافته لمحلول المحافظة.

Objectives: To investigate the effects of lidocaine on the morphology of saphenous veins (SVs) harvested during coronary artery bypass graft (CABG) surgery.

Methods: This experimental study was conducted at the Cardiovascular Surgery Department, Gazi University, Ankara, Turkey, between May and September 2007. The SVs from 11 patients who underwent CABG surgery were divided into 3 segments. Each segment from the same location of the grafts was allocated into 3 groups as control group (group C), physiologic saline group (group PS), and lidocaine group (group L). Nitric oxide synthase (NOS), nitric oxide (NO) pool, super oxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS) levels were measured in the samples from the groups. Histologic specimens were evaluated according to previously defined criteria, and scored accordingly.

Results: Histological examination of the grafts in groups L and C were similar, but histological scoring of grafts in group PS were statistically higher than group C (p=0.008). Nitric oxide synthase activity and NO pool were higher in groups L and PS than in group C (p=0.010). Super oxide dismutase activity was higher in group L than in group PS (p=0.008). Super oxide dismutase activity was lower in group PS than in group C (p=0.047). There was no significant difference between TBARS level in all groups.

Conclusion: Our results indicate that primary damage might occur during surgery due to traumatic handling of the graft, and succeeding injuries could occur due to ischemia-reperfusion injury during the waiting period. Adding lidocaine to the preservation solution will protect later injury.

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Autologous saphenous vein (SV) is the most commonly used conduit for coronary artery bypass surgery (CABG), however, it has a high occlusion rate.[1] Approximately 15-30% of the vein grafts occlude in the first year, and a total of 50% of the grafts eventually occlude within the 10-year period.[1] Vascular tissue injury, which occurs during harvesting due to traumatic handling of the graft was blamed for occlusion and failure of the bypass surgery. Ischemia reperfusion (I/R) injury of the graft is the second prominent factor leading to failure of the bypass surgery. Specific changes occur in the endothelium during I/R injury.[2] Formation of reactive oxygen species (ROS) and its effect on membrane lipids causes the lethal process on the endothelial cells of the graft.[2] Thiobarbituric acid reactive substances (TBARS) are end products of lipid peroxidation, which reflects inflammatory response and production of toxic oxygen metabolites.[3] Several preventive mechanism such as recombinant human superoxide dismutase (rhSOD), a free radical scavenger, and nitric oxide (NO) pathway, and nitric oxide synthase (NOS) activity limits the extent of the endothelial damage.[4,5] Properties of graft preservation fluid seem to be another important factor to ameliorate the extent of the damage on the vein grafts.[6] Several studies demonstrated that the choice of perioperative storage solution may influence the vascular reactivity of the human SV.[7] Vural et al[8] showed augmented NOS-2 expression in human SV grafts, when stored in ketotifen containing heparinized blood. The elevated NO level due to increased expression of NOS-2 improved vascular homeostasis in the venous graft. These results supported the suggestion of improving the long-term graft patency by increasing the NOS activity of the graft. Lidocaine is still largely used as a short-acting local anesthetic (LA) and antiarrhythmic agent. Due to its anti-inflammatory properties and significant effects on nonexcitable cells, recently, it has been used for the management of chronic inflammatory diseases.[9-11] Local anesthetics may also affect the production of superoxide anion in human neutrophils.[11] It has been hypothesized that toxic oxygen metabolites, generated by leukocytes during the inflammatory response could be one of the targets of LAs.[3] In light of this information, we hypothesized that adding lidocaine to the graft preservation solutions would have beneficial effects in the prevention of graft failure. In order to test this hypothesis, we investigated the NOS activities, SOD activities, NO pool, TBARS levels, and histological changes of the grafts.

Methods. In this study, 10 cm segments of SV grafts, harvested from 11 patients (between 39-75 years), who underwent CABG surgery at Gazi University Cardiovascular Surgery Department, Ankara, Turkey between May and September 2007 were used. Informed consents were obtained from the patients, and the study protocol was approved by the Ethical Committee of the university. Patients with diabetes mellitus, chronic renal failure, and patients using venoprotective drugs, and steroids were excluded from this study. Saphenous vein grafts were harvested with classical surgical techniques by the same surgeon. Distal 10 cm segments of the grafts were removed with atraumatical technique, and all branches of the segments were tied. A one cm segment was excised from the distal end of the harvested veins, and labeled as control group (group C). Half of these 1 cm segments were placed in 10% formalin solution for histologic evaluation. The other half was stored in -80^{0}C for biochemical analysis.

The remaining segments were divided into 2 parts, and one of them was immersed into lidocaine solution (5000 IU heparin + 50 ml physiologic saline + 5 ml 2% lidocaine [group L]), and the other part was immersed in physiologic saline solution (5000 IU heparin + 50 ml physiologic saline [group PS]). Then all segments were cannulated with a vessel canula, and distended to 100 mm Hg pressures for 2 minutes with the solutions in which they were placed. After distension, all grafts were kept in the particular solution for 45 minutes at room temperature. After this step, all segments of each group were divided into 2 parts for biochemical and histologic evaluation, as carried out in group C. The half of the vein graft samples for histologic evaluation were fixed in 10% buffered neutral formalin solution, and then dehydrated in increasing degrees of ethanol. Following staining with hematoxylin/eosin, the specimens were evaluated according to previously defined criteria,[12] and scored accordingly. The criteria for histologic evaluation and scoring were: 0 = no injury (**Figure 1**); 1 = minimal injury minimal endothelial desquamation, and minimal basal laminar separation (**Figure 2**), 2 = medium injury, medium endothelial desquamation and edema in media and intima (**Figure 3**), 3 = severe injury, extended endothelial desquamation, and extended edema formation in media and intima (**Figure 4**). The remaining half of the vein samples for biochemical analysis were washed with deionized cold water to discard blood. The tissues were homogenized in 4 volumes of ice-cold Tris-HCl buffer (50 mM, pH 7.4) for 2 minutes at 5000 rpm using a homogenizer (Diax 900, Heidolf Instruments GMBH and Company, Germany). The homogenate was centrifuged at 5000 g for 60 minutes to remove debris, and the clear upper supernatant fluid was taken. Thiobarbituric acid (TBA) reactive substances and protein levels were analyzed at this stage. The supernatant was extracted with an equal volume of an ethanol/chloroform mixture (5/3, v/v). After centrifugation at 5000 g for 30 minutes, the clear upper layer was taken, and used in the SOD, NOS activities, NO pool, and protein assays levels

were measured as described. The TBARS level was determined by a method based on the reaction with TBA at 90-100°C.[13] In the TBA test reaction, as a lipid peroxidation end product malondialdehyde (MDA) or MDA-like substances, and TBA react together for production of a pink pigment having an absorption peak at 532 nm, and the absorbance was read at this wavelength (UV-1601 Shimadzu Spectrophotometer, Japan). The results were expressed as nmol/mg protein according to a standard graphic, which was prepared with serial dilutions of standard MDA, for example, diethyl acetal. Thiobarbituric acid reactive substance levels were expressed as nmol/mg protein. Total SOD activity was determined according to the method of Durak et al.[14] One unit of SOD was defined as the enzyme amount causing 50% inhibition in the NBT reduction rate. Super oxide dismutase activity was also expressed as U/mg protein. The NOS activity and NO pool were determined according to the method of Durak et al.[15] Nitric oxide synthase activity method is based on the diazotization of sulfanilic acid by NO at acid pH, and subsequent coupling to N-(1-napthyl-ethylene diamine), which is the modification of Durak et al[15] study. Measurement of the NO pool (mainly consisting of NO + nitrite anion (NO_2^-) is also based on the same chemical reaction, in which to a greater extent NO, and to a lesser extent NO_2^-, but not nitrate anion (NO_3^-), give a diazotization reaction with sulfanilic acid. The absorbance of complexone formed with N-(1-naphthyl-ethylene diamine) reflects the sum of NO and NO_2-levels in the reaction medium, which is termed the NO pool in the present study. In this method, sodium nitroprusside is used as the chemical standard, and reaction scheme given for the NOS activity measurement, except for the incubation of the sample with arginine, is followed. Nitric oxide synthase activities and NO pool were expressed as IU/mg protein and protein amount by the Lowry method.[16] All the experiments were carried out at +4°C. The statistical analyses were carried out using SPSS 12.0 software program, and $p<0.05$ was considered

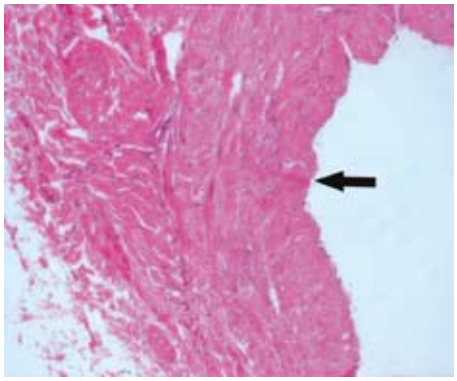

Figure 1 - Grade 0: Normal venous tissue; no injury (Hematoxylin and eosin x200)

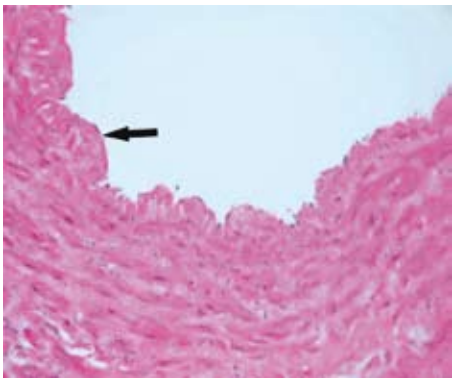

Figure 3 - Grade 2: medium injury, medium endothelial desquamation and edema in media and intima (Hematoxylin and eosin x200).

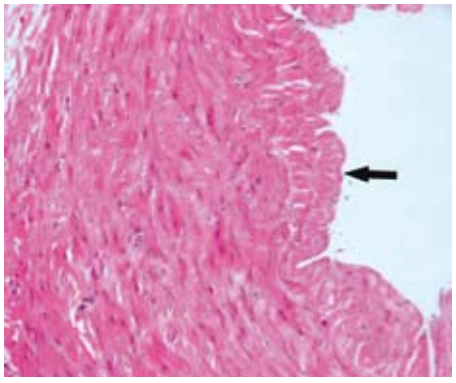

Figure 2 - Grade 1: minimal injury, minimal endothelial desquamation and minimal basal laminar separation (Hematoxylin and eosin x200).

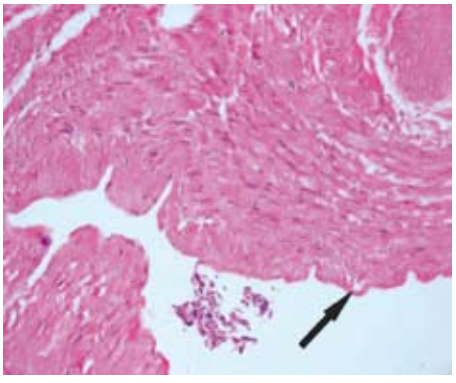

Figure 4 - Grade 3: severe injury (Hematoxylin and eosin x200).

statistically significant. The findings were expressed as mean ± standard deviation. The data were evaluated with Kruskal-Wallis variance analysis. The variables with significance were evaluated with Bonferroni corrected Mann-Whitney U test.

Results. Eleven patients (10 male, 1 female) with a mean (range) age of 60 ± 11.70 (39-75) years, height of 167±9.22 (150-180) and weight of 75.6±11.80 (48-90) were included. Histological finding of specimens preserved in group L and group C revealed similar results. However, specimens preserved in group PS revealed higher scores than in group C (p=0.010). Histological score of group C (n=11) was 1.09±0.94 (range 0-2), group L (n=11) 1.81 ± 0.75 (range 1-3) and group PS (n=11) 2.27 ± 0.78 (range 1-3). In group C, 2 specimens were found to have grade one, and 3 specimens were found to have grade 2 injuries, which indicate an early insult during harvesting stage. There were higher NOS activity and NO pool in group L (p=0.001), and in group PS (p=0.001) than in group C (p<0.05). Superoxide dismutase activity was higher in group L than in group PS (p=0.008). Superoxide dismutase activity of group PS was lower than group C (p=0.047). There was no significant difference between TBARS level of all groups (p=0.299) (**Table 1**).

Discussion. The causes of venous graft occlusion are not fully elucidated. The transition from venous to arterial position with shear stress, pulsatile flow, and high pressures are mostly blamed for this phenomena. Surgical handling of SV may cause functional, and morphologic injury on the endothelium that may progress into endothelial denudation. Hence, trauma of harvesting and preparation may contribute to events, which result in failure at both early and late stages.[6] The graft harvesting technique, preservation fluid, storage temperature, and the pressure applied to distend the vein graft seem to be important factors for the inflicted injury.[6,17]

In this study, we found that histopathological damage already occurs during harvesting of the SV before placing it into the preservation solutions. These injuries could be minimized through meticulous surgical techniques. Lidocaine solutions were found to be protective on SV endothelium when added to the preservative solutions. No statistically significant difference was found between the results of the specimens preserved in group L, and in group C. However, histologic scores of group PS were worse than in group C.

Another form of endothelial damage occurs in the I/R injury. Reactive oxygen radicals and their metabolites are known to play important roles in the pathogenesis of I/R injury.[18] The sign of this type of endothelial dysfunction is impaired endothelium-dependent vasodilation, namely, imbalance between NO synthesis and the production of ROS such as superoxide (O_2^-). The decrease of NO production and excessive O_2^- formation are the characteristic changes for dysfunctional endothelial cells.[19]

During conventional CABG, a high proportion of veins go into spasm at the time of harvesting. In order to overcome this, surgeons use vasodilators or high-pressure saline distension which may result, or aggravate endothelial damage and impair NO release. This was shown in various human and experimental studies.[1,5,7]

Nitric oxide plays an important role in maintaining vascular tone. Other beneficial properties of NO to vein graft patency include: the ability of NO to inhibit platelet aggregation, thrombus formation, leukocyte adhesion, and vascular smooth muscle cell proliferation.[1] The preservation of NO pathway and

Table 1 - Total nitric oxide synthase (NOS) activities (mIU/mg protein), nitric oxide (NO) pool (nmol/mg protein), superoxide dismutase (SOD) activities (U/mg protein), and thiobarbituric acid reactive substances (TBARS) (nmol/mg protein) of the groups. (Mean ± SD [minimum-maximum]).

Activities	Group C (n=11)	Group L (n=11)	Group PS (n=11)	‡*P*-value
NOS mean±SD (min-max)	10.13 ± 3.75 (5-18.3)	33.62 ± 19.21* (16.7-78.3)	46.92 ± 7.11*,† (30-55)	0.001
NO pool mean±SD (min-max)	43.33 ± 17.27 (16.7-75)	53.02 ± 5.04* (48.3-63.3)	39.38 ± 5.44† (33.3-50)	0.001
SOD mean±SD (min-max)	2.58 ± 0.94 (1.96-4.68)	3.60 ± 0.85* (2.52-5.14)	1.99 ± 0.38*,† (1.27-2.55)	0.047 0.008
TBARS mean±SD (min-max)	1.81 ± 0.92 (0.75-3.17)	1.26 ± 1.34 (0.15-3.61)	1.31 ± 0.32 (0.96-1.85)	0.299

*p<0.05 compared with group C, †p<0.05 compared with group L, ‡Kruskal-Wallis variance test

NOS activity are accepted as criteria for a clinically successful vein graft.[1,5,7] Several recent studies support the view that reduced expression of endothelial nitric oxide synthase (eNOS), and the consequent lower NO production, may be caused by the endothelial loss during the harvesting process. Tsui et al[5] demonstrated a reduced expression of eNOS in the endothelium of SVs harvested, according to the standard technique compared with SVs grafts harvested with a "no touch" technique. Chester et al[7] reported that segments of SV graft obtained during CABG operation and injected at a 300 mm Hg pressure, exhibited a reduced response to the endothelium-dependent dilatory effects of acetylcholine. These investigators attributed this finding to a reduced bioavailability of NOS in connection with areas of de-endothelization observed in this model of vein graft. In this study, we did not evaluate the levels of inducible NOs and eNOS separately. Instead, we measured the total NOS levels of the specimen, and assumed the results as the indicator of eNOS levels since the specimens are all vascular tissues.

In our study, NOS activity and NO pool values were higher in groups PS and L, than in group C. Higher NO pool values and NOS activity documented in groups PS and L, reflect the viability of endothelial function. Extensive oxidative stress following I/R injury initiates the lethal process in the endothelial cells.[2] Super oxide radicals are important precursors of H_2O_2, and other radical species including the hydroxyl radical. The hydroxyl radical also participates in lipid hyperoxidation.[18] The inhibition of leukocyte metabolism, and O_2^- formation by LAs has been well documented in several studies.[11,20] These direct scavenging effects of LAs have been attributed to various mechanisms. This evidence suggests that as LAs penetrate into the cell membranes, they interact with membrane lipids and proteins, to quench oxygen and NO free radical formation.[11] Lidocaine was reported to reduce the release of lipid peroxidation products from ischemic-reperfused myocardium.[21] Lipid peroxidation reflects the production of toxic oxygen metabolites, and it is a product of inflammatory response, and TBARS are end products of lipid peroxidation.[3] There was no significant difference between TBARS values for groups C, PS, and L in our study. However, SOD activity was higher in group L, than in groups C and PS. Increasing SOD activity, in group L is parallel to the increase in NOS and NO pool. Superoxides and high concentrations of NO reveal highly reactive peroxy nitrite, and this evidence indicates that high concentrations of peroxin nitrite are cytotoxic.[4] In the presence of normal TBARS values, SOD scavengers free oxygen radicals and SOD may inhibit the formation of peroxy nitrite, this may be an evidence for the protective effects of lidocaine during ischemia rather than any exacerbate inflammatory process. This was also evidenced by histological evaluations.

In conclusion, our results in group C stressed once more the importance of the meticulous handling of the graft tissue. Although group PS solution is known as an acceptable preservation solution for the SV grafts,[22] our results in the current study documented better results in both biochemical and histological parameters of the specimens in group L. These findings confirm the hypothesis that lidocaine may be beneficial as a preservative agent, when added to the standard serum physiologic solution. Our study was not largely population based, so this result may not be applicable to the general population. We believe further studies are required to determine the exact clinical benefits of these findings.

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Related topics

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