Comparison of transradial versus transfemoral diagnostic coronary angiography in terms of oxidative stress: Which option is more physiological?

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Abstract
In this randomized, single-center, clinical study we aimed to compare the oxidative stress response in patients undergoing diagnostic transradial or transfemoral elective coronary angiography. Sixty patients with stable angina pectoris undergoing elective coronary angiography to either transradial (n = 30) or transfemoral (n = 30) approach were included. The levels of plasma total oxidative status (TOS) were measured and compared just before and immediately after the procedure in both groups. The clinical and laboratory findings were compatible between the two groups. Although the levels of plasma total oxidative status after coronary angiography were increased in both groups (TF pTOS 20.5 ± 3; 34 ± 3 vs TR pTOS 18 ± 2; 23 ± 4), this was more pronounced in the transfemoral group as compared with the transradial group (ΔpTOS: 11 ± 4 vs 4 ± 3, p < 0.001). In correlation analysis, TOS levels and white blood cell counts (r = 0.25, p = 0.042), total cholesterol levels (r = 0.267, p = 0.041), triglyceride levels (r = 0.253, p = 0.049), serum creatinine levels (r = 0.260, p = 0.043) were found to be moderately positively correlated. This study showed that oxidative stress response associated with heart catheterization is more evident in patients undergoing transfemoral coronary angiography versus transradial coronary angiography.

Keywords
coronary angiography, oxidative stress, transfemoral, transradial

Introduction
Coronary artery disease (CAD) is the leading causes of death worldwide.1 Coronary angiography (CAG) is the current gold standard method to assess the presence of CAD.2 Peripheral arteries, such as femoral and radial artery are the most preferred access routes to perform diagnostic CAG.3 Many clinical trials and meta-analysis compared the transradial (TR) and transfemoral (TF) approach for diagnostic CAG showed that TR access is associated with lower risks of adverse outcomes such as cardiac death, bleeding, and access site complications.4 On the other hand, longer procedural durations associated with increased radiation exposure and technical failures raise concerns about TR CAG.5 During the diagnostic CAG, systemic and local inflammatory response have been demonstrated.6 Mechanical vascular damage induced by the insertion of the introducer sheath, aortic or coronary...
artery wall injury produced by the manipulation of catheters and injection of contrast agents are associated with the inflammatory response. Additionally, the dysfunction of microcirculation occurred by the reactive oxygen species (ROS) during the procedure might contribute to inflammatory response. A better understanding of the mechanisms that lead to ROS generation during CAG and the pathophysiological consequences of this process are important to improve the success rate of the procedure. The measurement of serum concentrations of various oxidants separately is not practical. It is time-consuming, complicated, expensive, and requires vigorous effort. Plasma total oxidative status (TOS) is an useful parameter to show the true levels of oxidative stress (OS).

In this study, we aimed to investigate the changes of OS in patients with stable angina pectoris (SAP) scheduled to undergo TR or TF diagnostic CAG.

Materials and methods

Patient characteristics

A total of 68 patients diagnosed with SAP undergoing elective CAG based on an appropriate functional non-invasive test for ischemia between the time period December 2019 and April 2020 were consecutively enrolled to this study in Istanbul University Cerrahpasa Institute of Cardiology (Institutional Trial Registry Number: 2019-121287). Patients diagnosed with acute coronary syndrome, chronic inflammatory disease, active malignancy, end-stage renal failure, previous coronary bypass surgery, abnormal Allen’s test result, history of iodinated contrast allergy, peripheral artery disease and left ventricular dysfunction (LVEF < 40%) and patients undergoing ad hoc percutaneous coronary interventions (PCI) were excluded from the study (Figure 1). Patients were randomized (1:1) to either TR or TFl access by a computer-based randomization system. The local ethics committee approved the study protocol (http://dogrulama.istanbulc.edu.tr/enVision.sorgula/belgedogrula.ama.aspx?V=BE6LEHKNC) and all patients provided their written informed consent.

Heart catheterization

TR CAG was performed by cannulating the right radial artery with a 6Fr, 10cm-long sheath (Radiofocus; Terumo Introducer II, Leuven, Belgium). Before sheath insertion a small (1 cc) amount of 1% lidocaine was injected into superficial skin. After sheath insertion, a radial cocktail including 0.2mg nitroglycerine and 5000 IU unfractionated heparin was given intra-arterially. Cordis Multipack catheters (Cordis, Johnson & Johnson) as JL 3.5 and JR4 were used for left heart catheterization. After the procedure, the sheath was removed immediately and a wrist clamp (TR band 18 mL; Terumo Europe NV, Leuven, Belgium) was applied for 2h. In patients undergoing TF CAG, right femoral artery was cannulated with a 6Fr, 11cm-long sheath (Avanti, Cordis, Johnson & Johnson). Before sheath insertion 10 cc 1% lidocaine was used for local anesthesia. Cordis Multipack catheters (Cordis, Johnson & Johnson) as JL 4 and JR4 were used for left heart catheterization. All patients received an intracoronary bolus of 0.2 mg nitroglycerine. After the procedure, hemostasis was achieved by manual compression for 30 min. The time between the insertion and removal of arterial sheath was calculated as procedural time. In both TR and TF CAG non-ionic, low osmolality (Omnipaque (Ioheksol); GE Healthcare, Cork, Ireland) contrast agent was used. All procedures were performed by the same two experienced invasive cardiologists.

Oxidative stress assessment

Peripheral venous blood samples of the patients were obtained from left antecubital vein into heparinized blood tubes before the radial or femoral arterial puncture and immediately after the withdrawal of diagnostic catheter. The plasma was separated by centrifugation at 3000 rpm for 10 min and stored at −80°C until the day of biochemical analysis. TOS was measured using a novel automated colorimetric method developed by Erel. In this method, oxidants present in the sample oxidize the ferrous ionodianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylene orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are
expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H₂O₂ Eq/L).

**Statistical analysis**

Our sample size calculation was based on a previous study demonstrating that 16–20 patients per each group should be included to detect a difference of 35% to 40% in inflammatory markers between patients undergoing TR and TF CAG with a 80% power and the conventional 5% two-sided type 1 error. Statistical Package for the Social Sciences software (SPSS, version 21, SPSS Inc, Chicago, IL, USA) was used for all statistical calculations. Continuous variables were presented as mean ± standard deviation or median with interquartile range as appropriate. Categorical variables are reported as frequency and percentage. Normal distribution was tested with the Kolmogorov Smirnov test. Comparison between categorical variables were evaluated using the Fisher’s exact test. The means for normally distributed continuous variables in the same group were compared by unpaired t-test. Continuous variables between the
two groups were compared using independent sample t-test. Pearson correlation test was used to indicate whether a statistically significant linear relationship exists between TOS levels and other continuous variables. A \( p \)-value of <0.05 was considered statistically significant.

**Results**

Sixty patients with SCAD were admitted to our study. Clinical, procedural and angiographic features of the patients are summarized in Tables 1 and 2. No significant differences was observed between the two study groups. All patients had a successful diagnostic procedure and no procedural complication was developed. According to the results of coronary angiography and clinical features of the patients, medical follow up in 22 patients (37%), coronary artery bypass surgery (CABG) in eight patients (13%) and percutaneous coronary interventions (PCI) in 30 patients (50%) were decided. Changes in TOS levels during the procedure are shown in Table 3. Although a significant increase was observed in both groups (TF \( \Delta pTOS \ 20 \pm 3; 34 \pm 3 \) vs TR \( \Delta pTOS \ 18 \pm 2; 23 \pm 4 \)), the TOS levels were more pronounced in TF group as compared with the TR group (\( \Delta pTOS \ 11 \pm 4 \) vs \( 4 \pm 3, \ p < 0.001 \)). In subgroup analysis, patients with type 2 diabetes mellitus (T2DM) in TF group also showed higher changes of TOS levels as compared with patients T2DM in TR group (\( \Delta pTOS \ 8 \pm 4 \) vs \( 4 \pm 3, \ p < 0.001 \)) In correlation analysis, TOS levels and white blood cell counts \( (r=0.25, p=0.042) \), total cholesterol levels \( (r=0.267, p=0.041) \), triglyceride levels \( (r=0.253, p=0.049) \), serum creatinine levels \( (r=0.260, p=0.043) \) were found to be moderately positively correlated.

**Discussion**

In this study, we observed that diagnostic heart catheterization induces an OS response and this alteration was significantly higher in patients undergoing TF CAG versus TR CAG. Our findings may have a clinical implication to explain the benefits of TR access over TF access by a molecular mechanism. Although there many publications reporting the clinical advantages of TR method, studies comparing the physiological changes caused by both methods are insufficient in the literature.\(^\text{11}\)

TF access has been the main option for many years in the diagnosis and treatment of CAD. There is an increasing trend around the cardiologists to prefer TR approach due to decreased vascular complications, bleeding events, and
improved patients convenience confirmed by randomized controlled trials. Currently, according to the many clinical practice guidelines, radial access is recommended as the standard approach for diagnostic and therapeutic coronary interventions unless there are overriding procedural considerations.

Systemic inflammatory response and impairment of circulatory endothelial function during heart catheterization have been demonstrated by Serafino et al. They showed that patients with SAP undergoing CAG to either TR or TF approach, both biomarkers of endothelial turnover (sE-Selectin) and systemic inflammation (hs-CRP) increased significantly in all patients. In this study sE-Selectin and hs-CRP levels were not different between the TR and TF groups at 24 h and 30 days respective time points. Yılmaz et al. reported that the oxidative stress response was significantly higher in patients with CAD compared with normal coronary arteries during diagnostic CAG. Iuliano et al. observed increased levels of F2-isprostanes, markers of lipid peroxidation in the coronary sinus of patients undergoing percutaneous coronary interventions but not in patients undergoing elective CAG. However, it should be taken into consideration that the group of CAG patients in that study consisted of only four patients. Almagor et al. demonstrated no changes in inflammatory markers in patients undergoing CAG. Golec et al. showed that the concentrations of malondialdehyde (MDA) and reduced glutathione (GSH) and the activities of Zn, Cu-superoxide dismutase (SOD-1), catalase (CAT), and cytosolic glutathione peroxidase (GSHPx) considered as biomarkers of oxidative

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**Table 2.** Laboratory and angiographic features of the study population.

| Laboratory values                  | Transfemoral group | Transradial group | p value |
|------------------------------------|--------------------|-------------------|---------|
| Hemoglobin, mg/dL                  | 13 ± 2             | 13 ± 3            | 0.934   |
| WBC, (10³/µL)                      | 8 ± 1              | 7 ± 2             | 0.300   |
| Platelet,* (10³/µL)                | 237 (198–281)      | 225 (194–281)     | 0.397   |
| Total cholesterol, mg/dL           | 178 ± 53           | 179 ± 40          | 0.954   |
| LDL-cholesterol, mg/dL             | 124 ± 51           | 121 ± 33          | 0.780   |
| HDL-cholesterol, mg/dL             | 45 ± 11            | 47 ± 11           | 0.618   |
| Triglyceride, mg/dL                | 146 ± 63           | 148 ± 60          | 0.903   |
| Fasting blood glucose,* mg/dL      | 120 (71–293)       | 116 (77–336)      | 0.692   |
| Creatinine,* mg/dL                 | 0.93 (0.80–1.17)   | 0.90 (0.71–0.97)  | 0.112   |
| CRP,* mg/dL                        | 2 (1–5)            | 2 (0.9–7)         | 0.958   |
| GFR, mL/min                        | 79 ± 22            | 83 ± 21           | 0.535   |
| Ejection fraction,* %              | 55 (48–60)         | 60 (50–60)        | 0.346   |
| Contrast volume,* mL               | 50 (40–75)         | 60 (50–80)        | 0.324   |
| Procedural time,* min              | 4 (3–5)            | 4 (3–7)           | 0.449   |
| Plasma TOS levels, (μmol H₂O₂ Eq/L). (before CAG) | 20 ± 3 | 18 ± 2 | 0.768 |
| Plasma TOS levels, (μmol H₂O₂ Eq/L) (after CAG) | 34 ± 3 | 23 ± 4 | 0.001 |
| Number of vessel disease, (n) (%)  | 0                  | 8 (27)            | 0.105   |
|                                    | 1                  | 10 (33)           |         |
|                                    | 2                  | 8 (27)            |         |
|                                    | 3                  | 4 (13)            |         |

CRP: C-reactive protein; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TOS: total oxidative status; WBC: white blood cell.

*Mann–Whitney U-test was used for non-normally distributed variables and expressed by the median-interquartile ranges.

**Table 3.** Comparison of plasma TOS levels before and after CAG.

|                  | Plasma TOS levels (before CAG) | Plasma TOS levels (after CAG) | Δ TOS levels | p < 0.001* |
|------------------|--------------------------------|-------------------------------|--------------|-------------|
| Transfemoral group | 20 ± 3                         | 34 ± 3                        | 14 ± 4       |             |
| Transradial group | 18 ± 2                         | 23 ± 4                        | 5 ± 3        |             |

CAG: coronary angiography; TOS: total oxidative status.

*Unpaired t-test was used to compare the plasma TOS levels before and after CAG in the same groups.
stress were significantly higher in elderly male SAP patients undergoing TF diagnostic CAG. Vassalle et al.\textsuperscript{20} determined that increased OS levels are associated with poor results in patients with CAD and they have stated that OS could be an important parameter to predict major adverse cardiac events (MACE) in this population. Sager and Nahrendorf\textsuperscript{21} demonstrated that inflammation initiated by leukocytes substantially contributes the destabilization of atherosclerotic plaques that causes acute coronary syndromes. Ryabov et al.\textsuperscript{22} observed that inflammation was a universal pathogenetic link between atherosclerosis and acute coronary syndrome.

The controversial results in the literature might be associated with the different study designs and the heterogeneity of the patient populations investigated. The higher occurrence of OS in TF CAG can be explained by some mechanisms. Primarily, the benefit of anticoagulation with heparin may suppress the level of OS increase in TR group. Skrzycki and Czeczot\textsuperscript{23} reported that heparin eliminates superoxide radicals from the cell environment and prevents the formation of reactive oxygen species and their derivatives by binding with a high affinity to certain antioxidant molecules. Borawski\textsuperscript{24} documented that heparin attenuates deleterious effects of myeloperoxidase in patients undergoing hemodialysis. In our opinion, in patients undergoing TF CAG, administration of heparin may reduce OS during the procedure. Additionally, mechanical vascular damage and distal microembolization induced by the manipulation of catheters may be exaggerated during TF CAG more than TR CAG considering the atherosclerotic burden of thoracoabdominal aorta. Our results indicate that diagnostic CAG induces an OS response and TR option seems to be more physiological compared with the TF option.

There are some limitations of this study. First, although the sample size was calculated and the power was adequate to detect possible differences between the two options, this study is a small pilot study. Second, the total antioxidant capacity (TAC) which is a component of the oxidative stress index was not calculated and the change of oxidative stress was carried out with a single measurement of TOS levels before and after the procedure. Third, the possible antioxidant effect of heparin in TR group should be taken into consideration. In addition, our population represents only patients with stable CAD undergoing diagnostic CAG and our findings may not generalized for different patient groups. Finally, the impact of our results on clinical outcomes require further validation by other studies.

**Conclusion**

In this study, we found that diagnostic CAG was associated with increased OS response and this response was significantly higher in patients undergoing TF approach. Further studies are necessary to understand the relationship between OS response associated with the different entry routes and clinical outcomes in daily practice.

**Author’s Note**

(*) The abstract of this study was accepted as a poster presentation at EuroPCR (The official annual meeting of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) on 19-22 May 2020, Paris.

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**Ethics approval**

Ethical approval for this study was obtained from Istanbul University Cerrahpasa Ethics Committee numbered as 121287 on the date of 7 August 2019. For confirmation you can visit http://dogrulama.istanbul.edu.tr/enVision.sorgula/belgedogrulama.aspx?V=BE6LEHKNC.

**Informed consent**

Written informed consent was obtained from all subjects before the study.

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