Association of Indicators of Dehydration and Haemoconcentration with the Coronary Slow Flow Phenomenon

Ramazan Kargin[1] MD, Yunus Emiroglu[1] MD, Selcuk Pala[1] MD, Mustafa Akcakoyun[1] MD, Soe Moe Aung[1] MD, Özkan Candan MD[1], Suzan Hatipoğlu[1] MD, Nihal Özdemir[1] MD.

[1] Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Department of Cardiology, Istanbul, Turkey

ABSTRACT

Objectives: The coronary slow flow phenomenon (CSFP), characterized by decreased distal progression of dye to coronary arteries, is a distinct angiographic phenomenon and little is known about its pathophysiology. Although several hypotheses have been suggested, the underlying mechanism of CSFP has not been well established yet. The aim of this study was to determine the roles of indicators of dehydration and haemoconcentration in CSFP which have blood flow abnormality effects.

Methods: The study consisted of 33 patients with CSFP (group 1), and 31 normal subjects as control group (group 2) detected by coronary angiography. CSFP was diagnosed by the TIMI frame count method. Serum electrolytes, osmolarity and haematological parameters were measured.

Results: Compared with control subjects, patient with CSFP had increased levels of calculated osmolarity, tonicity, sodium, glucose and blood urea nitrogen (BUN). Significant differences were also observed in the haematocrit, haemoglobin concentration, and calculated osmolarity but not in total cholesterol and albumin.

Conclusions: The results of the present study indicate that the markers of haemoconcentration and dehydration are significantly associated with CSFP. The markers may be important in the coronary blood flow anomaly.

Key Words: Coronary slow flow phenomenon, haematocrit, haemoconcentration, osmolarity, tonicity.

ÖZET

Koroner Yavaş Akım Fenomeniyle Dehidratasyon ve Hemokonsantrasyon Belirteçlerinin İlişkisi

Amaç: Patofizyolojik olarak az bilinen koroner yavaş akım fenomeni (KYAF) distal koroner arterin boyanma hızının azalması ile karekterize anjiografik bir fenomendir. Çeşitli hipotezler ileri sürülmüş olsada KYAF'nin mekanizması tam olarak açıklanmamıştır. Bu çalışmanın amacı dehitratasyon ve hemokonsantrasyon belirteçlerinin KYAF'de kan akım anomalisindeki rolünü belirlemektir.

Yöntemler: Çalışmaya anjiografik olarak 33 KYAF'si olan hasta (grup 1) ile 31 normal olan kontrol grubu hasta alınmıştır. KYAF tanısı TIMI frame sayım metodu ile konmuştur. Serum elektrolit, osmolarite, ve hematolojik parametreler ölçülmüştür.

Bulgular: KYAF hastalarında kontrol grubuna göre hesaplanmış osmolarite, tonisite, sodyum, glukoz, ve kan üre nitrojen düzeyi daha yüksek saptanmıştır. Ayrıca total kolesterol, albumin hariç hematokrit, hemoglobin ve hesaplanmış osmolarite de anlamlı fark saptanmıştır.

Sonuç: Bu çalışmamız KYAF ile hemokonsantrasyon ve dehitratasyon belirteçlerinin anlamlı olarak ilişkili olduğunu göstermiştir. Bu belirteçler koroner kan akım anomalisinde önemli olabilir.

Anahtar Kelimeler: Koroner yavaş akım fenomeni, hematokrit, hemokonsantrasyon, osmolarite, tonisite.

INTRODUCTION

The coronary slow flow phenomenon (CSFP), characterized by decreased distal progression of dye to coronary arteries, is a distinct angiographic phenomenon and little is known about its pathophysiology. Frequently, abnormally high small vessel resistance and increased microvascular tone have been suggested as the cause of this unique angiographic finding (1-3). It has been previously reported that brachial artery vascular endothelial functions are impaired in these patients (4). The vascular endothelium is injured by blood flow abnormalities aggravated by different risk factors. The viscoelastic nature of blood flow plays a major role in this process and depends on

Address for Reprints
Ramazan Kargın, MD.
Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Department of Cardiology, Istanbul
Telephone: +90 216 325 46 97 - 0505 565 33 25 **Fax:** +90 216 459 63 21 **e-mail:** ramazankargin@yahoo.com

corpuscular and biochemical components of the blood (5, 6).

Haemoconcentration describes conditions under which the relative ratio of cellular and biochemical blood components to plasma volume increases (7). Haematocrit (Hct), haemoglobin (Hb) and total protein concentrations are indirect parameters commonly used as indices of the degree of haemoconcentration (8, 9). In addition, serum osmolarity and sodium concentration are indicators of the status of extracellular fluid, as well as total body hydration (10, 11). It has been shown that haemorheological parameters, such as blood and plasma viscosity, Hct and Hb levels, are related to the incidence of cardiovascular disease (12-15)

Thus, in this study, we studied the relationship between the indicators of haemoconcentration and CSFP.

PATIENTS and METHODS

Thirty three patients (17 males and 16 females, mean age 51 ± 7 years, group 1) with CSFP detected by coronary angiography by the TIMI "frame count" method were included in this study. Gender and age-matched 31 control subjects with no coronary or valvular disease (15 males and 16 females, mean age 49 ± 8 years, group 2) were included in this study. In both groups, coronary arteriography was performed since the subjects were suffering from interactable symptoms such as angina and angina-like chest pain, shortness of breath and palpitation, and their symptoms could not be adequately clarified with noninvasive tests.

Exclusion criteria were as follows: coronary artery disease including spasm, plaque, ectasia or obstructive lesion, positive family history of hyperlipidemia, known peripheral vascular disease, diabetes mellitus, congestive heart failure, valvular heart disease, hypertrophic, restrictive and dilated cardiomyopathy, left ventricular hypertrophy, vasculitis, pulmonary, renal, and hematologic disorders and use of medications known to alter plasma lipid profile.

All participants underwent two-dimensional echocardiographic evaluation by an experienced research echocardiographer using commercially available echocardiography machines equipped with 3.5 MHz transducers (Vivid System Five, GE Vingmed Horten, Norway). Measurements were made according to the American Society of Echocardiography guidelines by a single cardiologist (16). Left ventricular ejection fraction (LVEF) was measured from the apical four-chamber and two-chamber views using the modified Simpson method (16).

Definition of Slow Coronary Flow

Coronary flow was quantified by using the thrombolysis in myocardial infarction (TIMI) frame count method (17). All patients with a TIMI frame count (TFC) greater than 2 standard deviations (SD) from the published normal range for the particular vessel were accepted as having CSFP while those whose TFC fell within 2 SD of the published normal range were considered to have normal coronary flow (17).

Measurement of TIMI Frame Count

Coronary angiography was performed via femoral approach using the standard Judkins technique and iopromide (Ultravist-370, Schering AG, Berlin, Germany) as the contrast agent (cine angiographic equipment: Philips Integris H 3000, Holland; cine frame:30 fps). The angiograms were recorded on a compact disc in DICOM format. We measured the number of cine frames required for the contrast to first reach standard distal coronary landmarks in the left anterior descending coronary artery (LAD), left circumflex artery (Cx), and right coronary artery (RCA). The first frame is defined as the one where the column of nearly or fully concentrated dye is seen extending across at least 70% of the arterial lumen with antegrade dye motion, and the last frame counted is that in which contrast first appears in the distal predefined landmark branch, but full opacification of the branch is not necessary (18). The distal coronary landmarks used for analysis were the distal bifurcation at the apex of the LAD (the mustache, pitchfork, or whale's tail), the distal bifurcation of the major obtuse marginal or the main Cx, whichever was larger, and the site of origin of first branch at the crux or its posterolateral extension for RCA. The cine film was run past the initial opacification of the end branch and then was moved frame by frame in reverse until the end branch disappeared before catching the last frame. Then the frame count for each artery was done by subtracting the first frame from the last frame. The LAD frame count was corrected by dividing with 1.7 to derive a corrected TIMI frame count (CTFC) (18).

Biochemical measurements

Blood samples were taken after overnight (12 h) fasting on the day prior to angiography. All measurements were performed on fresh serum. Serum lipids, were measured on a Roche Hitachi 911 (Roche Diagnostics, Indianapolis, IN, Germany) system using Roche cholesterol, Triglycerides/GB, LDL-C and HDL-C plus reagents.

The standard deviation for osmolarity measurements from triple samples was less than 1 mOsmol/kg H2O. sodium and potassium were determined by fully-selective system for Clinical Chemistry, ISE (Roche/Hitachi 902, Germany).

Serum osmolarity was calculated using the following equation: (10) Serum osmolarity= 1.897[Na^+] + glucose + BUN + 13.5 [19] where BUN is blood urea nitrogen. Serum glucose concentrations were determined by the enzymatic glucose oxidase method (Roche Hitachi analyzer), creatinine was determined by creatinine Roche Jaffe method (Roche/Hitachi 902) and urea was determined by the kinetic UV assay method (Hitachi/Roche Urea, Germany).

Statistical Analyses

Statistical analysis was performed with SPSS for Windows, version 16.0 (SPSS Inc. Chicago, Illinois). Data are presented as mean ± standard deviation. For continuous variables unpaired Student t test was used. A p value <0.05 was considered to indicate statistical significance.

RESULTS

The baseline characteristics of the study groups, TIMI frame count for each artery, in the use of antihypertensive medication are shown in Table 1.

Table 1: The baseline characteristics of the study groups, TIMI frame count for each artery, in the use of antihypertensive medication are shown.

	Group 1	Group 2	P value
Age, year	51 ± 7	49 ± 8	NS
Male/Female, n	17 / 16	15 / 16	NS
Heart rate, bpm	73 ± 7	69 ± 8	NS
Systolic BP, mmHg	120 ± 13	123 ± 12	NS
Diastolic BP, mmHg	79 ± 7	78 ± 9	NS
Smoking, n	12	10	NS
BMI, kg/mÇ	29±3	28±4	NS
LVEF, %	65 ± 3	66 ± 2	NS
CTFC-LAD, frames/sec	31±10	16±4	0.001
RCA TFC, frames/sec	33±9	15±4	0.001
Cx TFC, frames/sec	27±8	17±3	0.001
Mean TFC, frames/sec	30±7	16±3	0.001
Calcium antagonists, n	3	2	NS
ACE inhibitors, n	3	5	NS

BP; blood pressure, BMI; body mass index, LVEF; left ventricle ejection fraction, LDL; low-density lipoprotein, HDL; highe-density lipoprotein, CTFC-LAD; corrected TIMI frame count- Left anterior descending coronary artery, RCA TFC; right coronary artery TIMI frame count, Cx TFC; circumflex artery TIMI frame count.

The corrected TIMI frame count, Cx frame count, and RCA frame count were significantly higher in CSFP than control subjects. There was no difference between the two groups in terms of sex, age, heart rate, systolic blood pressure (BP), diastolic BP, body mass index (BMI), smoking, echocardiographic parameters and the use of angiotensin-converting enzyme inhibitors and calcium channel blockers.

The biochemical and haematological parameters of the study groups are shown in Table 2.

Table 2: The biochemical and haematological parameters of the study groups are shown.

	Group 1	Group 2	P value
Calculated osmolarity (mOsmol/kg H2O)	298.5± 9.2	286.1 ± 7.6	0.01
Serum tonicity (mOsmol/kg H2O)	295.2± 9.1	282.5 ± 7.4	0.001
Sodium (mEq/L)	139.8 / 3.6	137.4/ 4.5	NS
Potassium (mEq/L)	4.71 ±0.42	4.59 ± 0.35	NS
Glucose (mg/dL)	108 ± 20	100 ± 14	NS
BUN (mg/dL)	19.4 ± 6.7	16.2 ± 5.9	NS
Creatinine (mg/dL)	0.97 ±0.16	0.85± 0.19	NS
Haematocrit (%)	43.4±5.4	40.5±4.4	0.03
Haemoglobin (g/dL)	14.6 ± 1.7	13.8 ± 1.5	0.04
ESR (mm/h)	16±6	14 ±6	NS
Platelet count (X109/L)	242±89	258±53	NS
Partial prothrombin time (s)	27±2	26±3	NS
Prothrombin time (s)	12.6±2.5	11.6±1.2	NS
Total cholesterol (mg/dl)	194±36	187±42	NS
Triglycerides (mg/dl)	132±88	117±83	NS
LDL (mg/dl)	128± 29	121± 33	NS
HDL (mg/dl)	39±9	41±7	NS
Albumin (g/dl)	4.41±0.43	4.36±0.45	NS

The Hb values were 14.6±1.7 g/dL, 13.8±1.5 g/dL in groups 1, 2 respectively (p=0.04). The Htc values were 43.6±5.4 %, 40.5±4.4 % in groups 1, 2 respectively (p=0.03). The calculated serum osmolarity values were 298.5 ±9.2 mOsmol/kg H2O, 286.1±7.6 mOsmol/kg H2O in groups 1, 2 respectively (p=0.01). The serum tonicity values were 295.2 ±9.1 mOsmol/kg H2O, 282.1±7.4 mOsmol/kg H2O in groups 1, 2 respectively (p=0.001). Compared with control subjects, patients with CSFP had increased levels of serum Na^+, K^+, glucose, creatinine and BUN, but there was no significant difference between the two groups. There were no significant differences in the other biochemical parameters between the two groups.

DISCUSSION

The results of the present study indicated that some of the markers of haemoconcentration and dehydration are significantly associated with the CSFP. Although the pathophysiological mechanisms of CSFP remain uncertain, there are several hypotheses that have been suggested: for example, a form of early phase of atherosclerosis (20), small vessel dysfunction (21), Hagen–Poiseuille's equation model (22), imbalance between vasoconstrictor and vasodilatory factors (23-25), inflammation (26), platelet function disorder (27,28), and interaction of plasma homocysteine and thyroid hormone concentrations (29). It has also been reported that brachial artery vascular endothelial function was impaired in these patients (4).

Haematocrit, Hb, serum total protein, osmolarity, sodium, the density and viscosity of blood and plasma have been used as measures of the cellular and constituent mass to plasma volume ratio. However, the extent to which of these variables are indicative of haemoconcentration differs. Haematocrit and Hb concentration, routinely reported along with other haematological variables, are widely used as indices of haemoconcentration (8, 9). Because the Hct is the ratio of red cells to plasma volume, in order for the measure of Hct to provide an accurate estimate of changes in plasma volume, both a constant number of red blood cells and a constant volume of cells are assumed. Plasma or serum total protein concentration is also often measured concurrently with Hct and/or Hb to confirm haemoconcentration. Yet, total plasma protein is not sufficient by itself to estimate changes in plasma volume as accurately as Hct owing to the movement of small proteins across capillary membranes. Furthermore, because albumin is a negative acute-phase reactant and is reduced in cardiovascular disease patients, the total serum protein concentration does not increase significantly under these conditions.

In this study, we found for the first time that some of the haemoconcentration markers are significantly high in CSFP. High levels of some of the haemoconcentration markers have been reported to be associated with tachycardia (30), reduced oxygen transport (31), reduced myocardial perfusion (32) and increased risk of coronary thrombosis (33, 34).

Moreover, when red blood cells (RBCs) pass through the microcirculation, they release vasodilatory compounds, such as ATP or nitric oxide (NO), that enhance blood flow to hypoxic tissues (35,36) causing the imbalance between vasoconstrictor and vasodilatory mechanisms.

In our study, increased TFC values in patients with CSFP might be caused by cardiac effects of haemoconcentration markers.

The findings of the present study indicated that CSFP patients have statistically significant dehydration when compared to control subjects. The results showed that serum osmolarity was increased in CSFP patients.

The major determinants of serum osmolarity, namely sodium, glucose and BUN, were higher in SCFP patients although it was statistically insignificant. Even though serum osmolarity and sodium are indicators of the hydration status of the body, their relationship is influenced by glucose and BUN, as seen in equation 1. The effect of sodium on cardiovascular disease is mainly exerted through its effects on blood pressure (37). However, recent animal studies, as well as clinical/therapeutic trials, have shown that Na^+ has pressure-independent injurious effects on the arterial wall (37, 38). Most outcomes in diabetes mellitus patients are due to insulin insufficiency, but hyperglycaemia itself, as an independent variable, has deleterious effects, such as glycosylation of tissue proteins and hyperosmolarity (39, 40).

Few prospective studies of CAD risk have evaluated the coagulation activation markers, and shortened coagulation times, were thereafter limited and inconclusive (41, 42).

In our study, platelet count, partial prothrombin time and prothrombin time were similar in both groups.

The Thrombolysis in Myocardial Infarction (TIMI) flow grading system is a valuable and widely used qualitative measurement for CSFP. However, the measurement of TFC from coronary angiograms is operator-dependent to some extent. Important variables that can significantly affect the TFC exist. For example, nitrate use, heart rate, and the phase of the cardiac cycle in which dye is injected have a significant effect on TFC (43). The corpuscular and biochemical components play a major role the viscoelastic nature of blood flow (5, 6).

Some of dehydration and haemoconcentration marker should be taken into account when using TFC method in conditions which are responsible for CSFP such as myocardial microvascular disorder and endothelial dysfunctions.

Study Limitations

Whole-blood and plasma viscosity were not examined in the present study. Coronary blood flow was not measured invasively.

CONCLUSION

In conclusion, the results of the present study indicate that the markers of haemoconcentration and dehydration are significantly associated with CSFP. The markers may be important in the coronary blood flow anomaly.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E: Angina pectoris and slow flow velocity of dye in coronary arteries. A new angiographic finding. Am Heart J 1972; 84:66-71.

2. Mosseri M, Yarom R, Gotsman MS, Hasin Y: Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986; 5:964-972.

3. Mangieri E, Macchiarelli G, Ciavolella M, Barillà F, Avella A, Martinotti A, et al: Slow coronary flow: Clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovase Diagn. 1996; 37(4): 375-81.

4. Sezgin AT, Sigirci A, Barutcu I, Topal E, Sezgin N, Ozdemir R, et al: Vascular endothelial function in patients with slow coronary flow. Coronary Artery Dis 2003; 14:155-161.

5. Lowe GD, Rumley A, Whincup PH, Danesh J. Hemostatic and rheological variables and risk of cardiovascular disease. Semin Vasc Med 2002; 2: 429–39.

6. Danesh J, Collins R, Peto R, Lowe GD. Haematocrit, viscosity, erythrocyte sedimentation rate: Meta-analyses of prospective studies of coronary heart disease. Eur Heart J 2000; 21: 515–20.

7. Hell KM, Balzereit A, Diebold U, Bruhn HD. Importance of blood viscoelasticity in arteriosclerosis. Angiology 1989; 40: 539-46.

8. Costill DL, Fink W. Plasma volume changes following exercise and thermal dehydration. J Appl Physiol 1974; 37: 521–5.

9. Greenleaf JE, Convertino VA, Mangseth GR. Plasma volume during stres in man: Osmolarity and red cell volume. J Appl Physiol 1979; 47: 1031–8.

10. Rasouli M, Kalantari KR. Comparison of methods for calculating serum osmolarity: Multivariate linear regression analysis. Clin Chem Lab Med 2005; 43: 635–40.

11. Kumar S, Berl T. Sodium. Lancet 1998; 352: 220–8.

12. Kesmarky G, Toth K, Habon L, Vajda G, Juricskay I. Hemorheological parameters in coronary artery disease. Clin Hemorheol Microcirc 1998; 18: 245–51.

13. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease: The Framingham study. A 34-year followup. Am Heart J 1994; 127: 674–82.

14. Sorlie PD, Garcia-Palmieri MR, Costas R, Havlik RJ. Hematocrit and risk of coronary heart disease: The Puerto Rico Health Program. Am Heart J 1981; 101: 456–61.

15. Arant CB, Wessel TR, Olson MB, Bairey Merz CN, Sopko G, Rogers WJ, et al. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain. J Am Coll Cardiol. 2004; 43: 2009–14.

16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H. et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.

17. Gibson CM, Cannon CP, Delay WL: TIMI frame count. A quantitative method of assessing coronary artery flow. Circulation 1996; 93:879-883.

18. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93:879-88.

19. Lente FV. Markers of inflammation as predictors in cardiovascular disease. Clin Chim Acta 2000; 293: 31–52.

20. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation 1986;74:964–72.

21. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteriesa new angiographic finding. Am Heart J 1972;84:66–71.

22. Rim SJ, Leong-Poi H, Lindner JR, Wei K, Fisher NG, Kaul S. Decrease in coronary blood flow reserve during hyperlipidemia is secondary to an increase in blood viscosity. Circulation 2001;104:2704–9.

23. *Pekdemir H, Polat G, Cin VG, Camsari A, Cicek D, Akkus MN, et al. Elevated plasma endothelin-1 levels in coronary sinus during rapid right atrial pacing in patients with slow coronary flow. Int J Cardiol 2004;97:35–41.*
24. *Camsari A, Pekdemir H, Cicek D, Polat G, Akkus MN, Döven O, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. Circ J 2003;67:1022–8.*
25. *Sezgin N, Barutcu I, Sezgin AT, Gullu H, Turkmen M, Esen AM, et al. Plasma nitric oxide level and its role in slow coronary phenomenon. Int Heart J 2005;46:373–82.*
26. *Jian-Jun Li, Bo Xu, Zi-Cheng Li, Jie Qian, Bing-Qi Wei. Is slow coronary flow associated with inflammation? Medical Hypotheses 2006;66:504–8*
27. *Lanza GA, Andreotti F, Sestio A, Sciahbasi A, Crea F, Maseri A. Platelet aggregability in cardiac syndrome X. Eur Heart J 2001;22:1924–30.*
28. *Gokce M, Kaplan S, Tekelioglu Y, Erdoğan T, Küçükosmanoğlu M. Platelet function disorder in patients with coronary slow flow. Clin Cardiol 2005;28:145–8.*
29. *Evrengul H, Tanriverdi H, Enli Y, Kuru O, Seleci D, Bastemir M, et al. Interaction of Plasma Homocysteine and Thyroid Hormone Concentrations in the Pathogenesis of the Slow Coronary Flow Phenomenon. Cardiology 2007;108:186–192*
30. *Julius S, Palatini P, Nesbitt SD. Tachycardia: an important determinant of coronary risk in hypertension. J Hypertens Suppl 1998;16:S9–15.*
31. *Finch CA, Lenfant C. Oxygen transport in man. N Engl J Med 1972;286:407–15.*
32. *Becker RC. Seminars in thrombosis, thrombolysis, and vascular biology. Part 5. Cellular-rheology and plasma viscosity. Biorheology 1991;79:265–70.*
33. *Koenig W, Ernst E. The possible role of hemorheology in atherothrombogenesis. Atherosclerosis 1992;94:93–107.*
34. *Yasaka M, Yamaguchi T, Oitia J, Sawada T, Shichiri M, Omae T, et al. Clinical features of recurrent embolization in acute cardioembolic stroke. Strong disposing factors: low plasma levels of antithrombin II. Stroke 1993;24:1681–5.*
35. *Ellsworth ML, Forrester T, Ellis CG, Dietrich HH. The erythrocyte as a regulator of vascular tone. Am J Physiol. 1995 Dec; 269(6 Pt 2): H2155-61.*
36. *Cosby K, Partovi KS, Crawford JH, Patel RP, Reiter CD, Martyr S, Yang BK, Waclawiw MA, Zalos G, Xu X, Huang KT, Shields H, Kim-Shapiro DB, Schechter AN, Cannon RO 3rd, Gladwin MT. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med. 2003 Dec;9(12):1498-505.*
37. *Gonzalez-Albarran O, Ruilope LM, Villa E, Robles RG. Salt sensitivity: Concept and pathogenesis. Diabet Res Clin Pract 1998; 39 (Suppl.): S15–26.*
38. *Safar ME, Thuilliez CH, Richard V, Benetos A. Pressure-independent contribution of sodium to large artery structure and function in hypertension. Cardiovasc Res 2000; 46: 269–76.*
39. *Haffner SJ, Cassells H. Hyperglycemia as a cardiovascular risk factor. Am J Med 2003; 115: S6–11.*
40. *Hoogwerf BJ, Sprecher DL, Pearce GL, Acevedo M, Frolkis JP, Foody JM, et al. Blood glucose concentrations < 125 mg/dL and coronary heart disease risk. Am J Cardiol 2002; 89: 596–9.*
41. *Lowe GDO, Rumley A, Sweetnam P, Yarnell JWG, RumleyJ. Fibrin D-dimer, markers of coagulation activation, and the risk of major ischaemic heart disease in the Caerphilly Study. Thromb Haemost 2001;86:822–827*
42. *Cooper JA, Miller GJ, Bauer KA, Morrissey JH, Meade TW, Howarth DJ, et al. Comparison of novel haemostatic factors and conventional risk factors for prediction of coronary heart disease. Circulation 2000;102:2816–2822*
43. *Abaci A, Oguzhan A, Eryol NK, Ergin A. Effect of Potential Confounding Factors on the Thrombolysis in Myocardial Infarction (TIMI) Trial Frame Count and Its Reproducibility Circulation 1999;100;2219-2223*