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Biomarkers for cardiovascular diseases: their clinical significances and future directions

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by

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Abstract

Biomarkers are used for evaluation of the pathophysiological state, risk stratification, diagnostic tools, staging of a disease and responsiveness to treatment. Representative biomarkers used in cardiovascular diseases may include C-reactive protein (CRP) for inflammation, brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), aldosterone, renin for neurohumoral factors, plasminogen activator inhibitor type-1 (PAI-1) for fibrinolysis and endothelial function, d-dimer for thrombosis, urine albumin /creatin ratio for renal glomerular endothelial function. Further addition of new biomarkers may increase the capacity to find high-risk patients with cardiovascular diseases. In this review we would like to introduce several representative biomarkers in the context of nuclear cardiology. With the advancement of new imaging modalities new biomarkers are readily available. Combined use of new nuclear cardiology modalities with biomarkers one would establish prevention guidelines and classify high-risk subgroups needing treatment intervention.

The concept of biomarkers

The concept of a biomarker is defined as “a characteristic marker that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (1). They are used for evaluation of the pathophysiological state, risk stratification, diagnostic tools, staging of a disease and responsiveness to treatment. Representative biomarkers used in cardiovascular diseases may include C-reactive protein (CRP) for inflammation, brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), aldosterone, renin, norepinephirine and thyroid hormones (free T3; FT3, free T4; FT4) for neurohumoral factors (2), plasminogen activator inhibitor type-1 (PAI-1) for fibrinolysis and endothelial function, d-dimer for thrombosis, urine albumin /creatin ratio for renal glomerular endothelial function. Addition of new biomarkers may increase the capacity to find high-risk patients with cardiovascular diseases. In this review we would like to introduce several representative biomarkers in the context of nuclear cardiology. Representative biomarkers of cardiovascular diseases are listed in Table 1 and the relationships between vascular injury and representative biomarkers are shown in Figure 1.

Pro-inflammatory cytokines

Cytokine is a collective term for functional proteins produced by cells as messengers. Interleukin (IL)-6 is a multifunctional cytokine that regulates immune responses and induces acute phase response (3). IL-6 may represent critical pathophysiologic inflammatory activities. Overproduction of IL-6 is involved in chronic inflammatory diseases, including atherosclerotic cardiovascular diseases (4). IL-6 has been investigated as a potential biomarker of vascular diseases. Previous studies have shown that serum IL-6 levels were related to cardiovascular risk factors and coronary heart disease (5). The receptor for IL-6 is also a target of prevention of coronary vascular diseases (6). Conversely, the relationship between inflammatory markers and myocardial single photon emission computed tomography (SPECT) findings remains somewhat controversial (7).

Endothelin-1

Endothelin-1 is a peptide vasomodulator produced by endothelial cells, macrophages and fibroblasts (8). Endothelin-1 has critical roles for proliferative vascular diseases such as pulmonary arterial hypertension (PAH). Endothelin-1 expression is induced by pro-fibrotic growth factor transforming growth factor (TGF)-β. Its signaling via the endothelin receptor type A and type B stimulates fibroblast migration, myofibroblast differentiation and proliferation of smooth muscle cells. Endothelin-1 induces vasoconstriction mainly through endothelin receptor type A. Antagonists of endothelin-1 receptor are effective for PAH. Plasma levels of endothelin-1 have been reported to be elevated and a positive correlation was found between endothelin-1 levels and systolic pulmonary arterial pressure. Plasma levels of endothelin-1 can be used in conjunction with other modalities to

evaluate PAH (9).

ADMA

Vascular endothelial cells produce nitric oxide (NO). NO is a vasodilator and lowers blood pressure. NO production is mediated by NO synthase using arginine as substrate. Asymmetric N^G, N^G-dimethylarginine (ADMA= Asymmetric dimethylarginine) is an endogenous NO synthase inhibitor (10). When ADMA accumulates in endothelium, NO synthesis is inhibited and endothelial dysfunction is induced, leading to hypertension and vascular diseases. ADMA is a biomarker of endothelial function and its concentration is increased in hypertension, diabetes, dyslipidemia and chronic kidney disease (11). As assessed by ^{11}C-acetate positron-emission tomography (PET) the right ventricle (RV) oxidative metabolic rate was increased inpatients with pulmonary hypertension (PH). Patients with World Health Organization functional class II/III PH also had increased RV power and efficiency. In these patients with increased pulmonary arterial pressure, ADMA and BNP were increased (12).

PAI-1

PAI-1 is the physiologic inhibitor of fibrinolysis. The fibrinolytic activity in plasma is based on fine balance between PAI-1 and tissue-type plasminogen activator (t-PA). Increase in plasma PAI-1 concentration is associated with recurrent coronary events in survivors of acute myocardial infarction. Elevated PAI-1 activity is associated with coronary microvascular dysfunction as assessed by ^{15}O-water PET (13). PAI-1 deficient mice exhibit no apparent abnormalities. However, PAI-1 deficiency in humans can cause severe bleeding tendency and impairment of wound healing (14), suggesting an important role of PAI-1 in thrombosis and hemostatsis in humans.

PAI-1 is also involved in tissue remodeling by inhibiting activities of matrix metalloproteinases and urokinase-type plasminogen activators (uPA). In experimental studies expression of PAI-1 in heart is correlated with fibrotic changes (15). In vessels angiotensin receptor blocker suppresses the expression of PAI-1 (16). Enhanced PAI-1 expression may contribute to ventricular remodeling through attenuation of extracellular matrix degradation.

Cardiac troponin

Troponin forms a protein complex consisting of troponin C (TnC), toponin I (TnI), and troponin T (TnT) in myocytes and skeletal muscles. Troponin is involved in the regulation of muscle contraction through calcium handling between actin and myosin. Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have characteristic amino acid sequences different from skeletal counterparts. Thus, cTnI and cTnT are specifically detected through immunoassays and they are clinically widely used as biomarkers representing myocyte injury in addition to creatine kinase

isoform MB (CK-MB) and heart-type fatty acid binding protein. More than 90% of cardiac troponin resides in myocyte structural filaments and only a few % are in cytoplasm. Upon reversible myocyte injury cardiac troponin is released from cytoplasm. With irreversible injury such as acute myocardial infarction (AMI) cardiac troponin is released from the structural filaments to circulation. With the availability of highly sensitive troponin assays AMI can be detectable within 2 hours from the onset. In particular with non-ST-segment elevation MI increase in troponin above cut-off values can be detected before electrocardiogram (ECG) changes occur.

Independent predictors of measurable SPECT-myocardial perfusion imaging (MPI) infarct size include cTnT at days 1, 2, 3 and peak cTnT. A cut-off value of peak cTnT of 1.5 ng/ml is suggested for the detection of measurable infarct (17). Furthermore, in chronic heart failure myocyte apoptosis may be constantly increased and cardiac troponin tends to be elevated. Circulating troponin concentration is therefore useful for evaluation of severity of heart failure and is used as an index for assessing prognosis. Newer biomarkers have arrived and are becoming part of routine care of heart failure patients. Impaired coronary flow reserve derived from ^{82}Rb-PET is associated with elevated troponin and major cardiac events (18), implicating the important relationship between biomarkers and nuclear cardiology. It is also indicated that the combination of troponin T and myocardial ^{99m}Tc-sestamibi scintigraphy is the best model for early prediction of cardiac events in acute chest pain patients (19). These studies strongly demonstrated the close association between biomarkers and nuclear cardiology and the combined use of these two modalities are useful tools for diagnosis, risk stratification and predications of clinical events.

Biomarkers of pulmonary arterial hypertension

The natriuretic peptides are used for diagnosis and evaluation of heart failure. BNP and N-terminal prohormone of BNP (NT pro-BNP) are produced and released from cardiac ventricular myocytes and reflect myocardial responses to stretch. It is well-known that BNP or NT pro-BNP is an important biomarker to assure prognosis in patients with left ventricular heart failure in addition to detect the prevalence of cardiac failure. In addition, BNP is also an important marker for assuring the prevalence of right ventricular failure. They are also used for risk stratification and heart failure management. PAH can become life-threatening if pulmonary vascular damages progress. At the moment there are no validated biomarkers useful for diagnosis of PAH. For evaluation of PAH severity levels of BNP and NT pro-BNP are reported as useful. Because they tend to increase with early phase of PAH and correlate with pulmonary arterial pressure (20). Scleroderma patients with NT pro-BNP levels exceeding 395 pg/mL are likely to suffer from pulmonary hypertension (21). Changes of NT pro-BNP levels may estimate prognosis. NT-proBNP is one of the prognostic factors in pediatric PAH (22). Thus, plasma levels of BNP and NT pro-BNP are included as parameters for assessing disease severity, stability and prognosis of PAH in the treatment guidelines of the Task

Force for the Diagnosis of Treatment of PAH of the European Society of Cardiology and European Respiratory Society (23). Using PET the role of metabolic alterations in the development of a maladaptive right ventricular response in PAH was recently evaluated (24). Abnormalities in fatty acid metabolism may be detected in the blood and myocardium in human PAH and may serve as biomarkers associated with cardiac steatosis or lipotoxicity.

Future directions

Prevalence of cardiovascular disease is high. Risk stratification using appropriate biomarkers and subsequent risk control are important and useful. With the advancement of new imaging modalities (25) such as coronary artery disease (26, 27) and heart failure (28) new biomarkers are readily available. Combined use of new nuclear cardiology modalities with biomarkers one would establish prevention guidelines and classify subgroups needing effective and efficient treatment intervention. For physicians, the capability to utilize and appropriately interpret these biomarkers is imperative to the care of cardiac patients, particularly as these newer biomarkers become widely used.

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Conflict of interest

None

References

1. The National Institutes of Health Biomarkers Definitions Working group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001; 69: 89-95.
2. Pingitore A, Nicolini G, Kusmic C, Iervasi G, Grigolini P, Forini F. Cardioprotection and thyroid hormones. Heart Fail Rev 2016 [Epub ahead of print]
3. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol 2015; 16: 448-57.
4. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. Atherosclerosis 1996; 127: 263-71.
5. Mendall MA, Patel P, Asante M, Ballam L, Morris J, Strachan DP, Camm AJ, Northfield TC.

Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart 1997; 78: 273-7.

6. Interleukin 6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet 2012; 379: 1214-1224.
7. Fleming RM1, Harrington GM. What is the relationship between myocardial perfusion imaging and coronary artery disease risk factors and markers of inflammation? Angiology 2008; 59: 16-25.
8. Vignon-Zellweger N, Heiden S, Miyauchi T, Emoto N. Endothelin and endothelin receptors in the renal and cardiovascular systems. Life Sci 2012; 91: 490-500.
9. Fahmy EM, Abdelraouf DA. Right ventricular myocardial isovolumic relaxation time as novel method for evaluation of pulmonary hypertension: correlation with endothelin-1 levels. J Am Soc Echocardiogr 2007; 20: 462-9.
10. Konya H, Miuchi M, Satani K, Matsutani S, Yano Y, Tsunoda T, Ikawa T, Matsuo T, Ochi F, Kusunoki Y, Tokuda M, Katsuno T, Hamaguchi T, Miyagawa J, Namba M. Asymmetric dimethylarginine, a biomarker of cardiovascular complications in diabetes mellitus. World J Exp Med 2015; 5: 110-119.
11. Böger RH. The pharmacodynamics of L-arginine. J Nutr 2007; 137: 1650S-1655S.
12. Yoshinaga K , Ohira H, Tsujino I, Oyama-Manabe N, Mielniczuk L, Rob S. B. Beanlands, Chietsugu Katoh, Katsuhiko Kasai, Osamu Manabe, Takahiro Sato, Satoshi Fujii, Yoichi M. Ito, Yuuki Tomiyama, Masaharu Nishimura, Nagara Tamaki. Attenuated right ventricular energetics evaluated using ^{11}C-acetate PET in patients with pulmonary hypertension. Eur J Nucl Med Mol Imaging 2014; 41:1240-1250.
13. Naya M, Tsukamoto T, Inubushi M, Morita K, Katoh C, Furumoto T, Fujii S, Tsutsui H, Tamaki N. Elevated plasma plasminogen activator inhibitor type-1 is an independent predictor of coronary microvascular dysfunction in hypertension. Circ J 2007; 71: 348-53.
14. Iwaki T, Tanaka A, Miyawaki Y, Suzuki A, Kobayashi T, Takamatsu J, Matsushita T, Umemura K, Urano T, Kojima T, Terao T, Kanayama N. Life-threatening hemorrhage and prolonged wound healing are remarkable phenotypes manifested by complete plasminogen activator inhibitor-1 deficiency in humans. J Thromb Haemost 2011; 9: 1200-1206.
15. Zaman AK, French CJ, Schneider DJ, Sobel BE. A profibrotic effect of plasminogen activator inhibitor type-1 (PAI-1) in the heart. Exp Biol Med (Maywood) 2009; 234: 246-54.
16. French CJ, Zaman AK, Sobel BE. The angiotensin receptor blocker, azilsartan medoxomil (TAK-491), suppresses vascular wall expression of plasminogen activator inhibitor type-I protein potentially facilitating the stabilization of atherosclerotic plaques. J Cardiovasc Pharmacol 2011; 58: 143-8.

17. Arruda-Olson AM, Roger VL, Jaffe AS, Hodge DO, Gibbons RJ, Miller TD. Troponin-T levels and infarct size by SPECT myocardial perfusion imaging: a prospective evaluation JACC Cardiovasc Imaging 2011; 4: 523-533.
18. Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 2015; 131: 528-35.
19. Swinburn JM, Stubbs P, Soman P, Collinson P, Raval U, Senior R, Lahiri A. Rapid assessment of patients with non-ST-segment elevation acute chest pain: troponins, inflammatory markers, or perfusion imaging? J Nucl Cardiol 2002; 9: 491-9.
20. Dentali F, Donadini M, Gianni M, Bertolini A, Lonn E, Venco A, Cattozzo G, Ageno W. Brain natriuretic peptide as a preclinical marker of chronic pulmonary hypertension in patients with pulmonary embolism. Intern Emerg Med 2009; 4: 123-8.
21. Williams MH, Handler CE, Akram R et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006; 27: 1485–1494.
22. Ploegstra MJ, Zijlstra WM, Douwes JM, Hillege HL, Berger RM. Prognostic factors in pediatric pulmonary arterial hypertension: A systematic review and meta-analysis. Int J Cardiol. 2015; 184:198-207.
23. Galie N, Hoeper MM, Humbert M et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009; 30: 2493–2537.
24. Ohira H, deKemp R, Pena E, Davies RA, Stewart DJ, Chandy G, Contreras-Dominguez V, Dennie C, Mc Ardle B, Mc Klein R, Renaud JM, DaSilva JN, Pugliese C, Dunne R, Beanlands R, Mielniczuk LM. Shifts in myocardial fatty acid and glucose metabolism in pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response. Eur Heart J Cardiovasc Imaging 2015 [Epub ahead of print]
25. Yoshinaga K. Time to move on to the next stage and open our door to the world. Ann Nucl Cardiol 2015; 1: 1-2.
26. Tanaka H, Chikamori T, Hida S, Igarashi Y, Shiba C, Usui Y, Hatano Y, Yamashina A. Diagnostic value of vasodilator-induced left ventricular dyssynchrony as assessed by phase analysis to detect multivessel coronary artery disease. Ann Nucl Cardiol 2015; 1: 6-17.
27. Sato A, Makiguchi N, Narita K, Hasebe N. Cardiovascular imaging for nuclear cardiologists: First step of coronary computed tomography angiography. Ann Nucl Cardiol 2015; 1: 69-76.

28. Kasama S, Toyama T, Kurabayashi M. The clinical usefulness of cardiac sympathetic nerve imaging using 123Iodine-Meta-iodobenzylguanidine scintigraphy to evaluate the effectiveness of pharmacological treatments in patients with heart failure. Ann Nucl Cardiol 2015; 1: 117-126.

Table 1. Representative biomarkers of cardiovascular diseases.

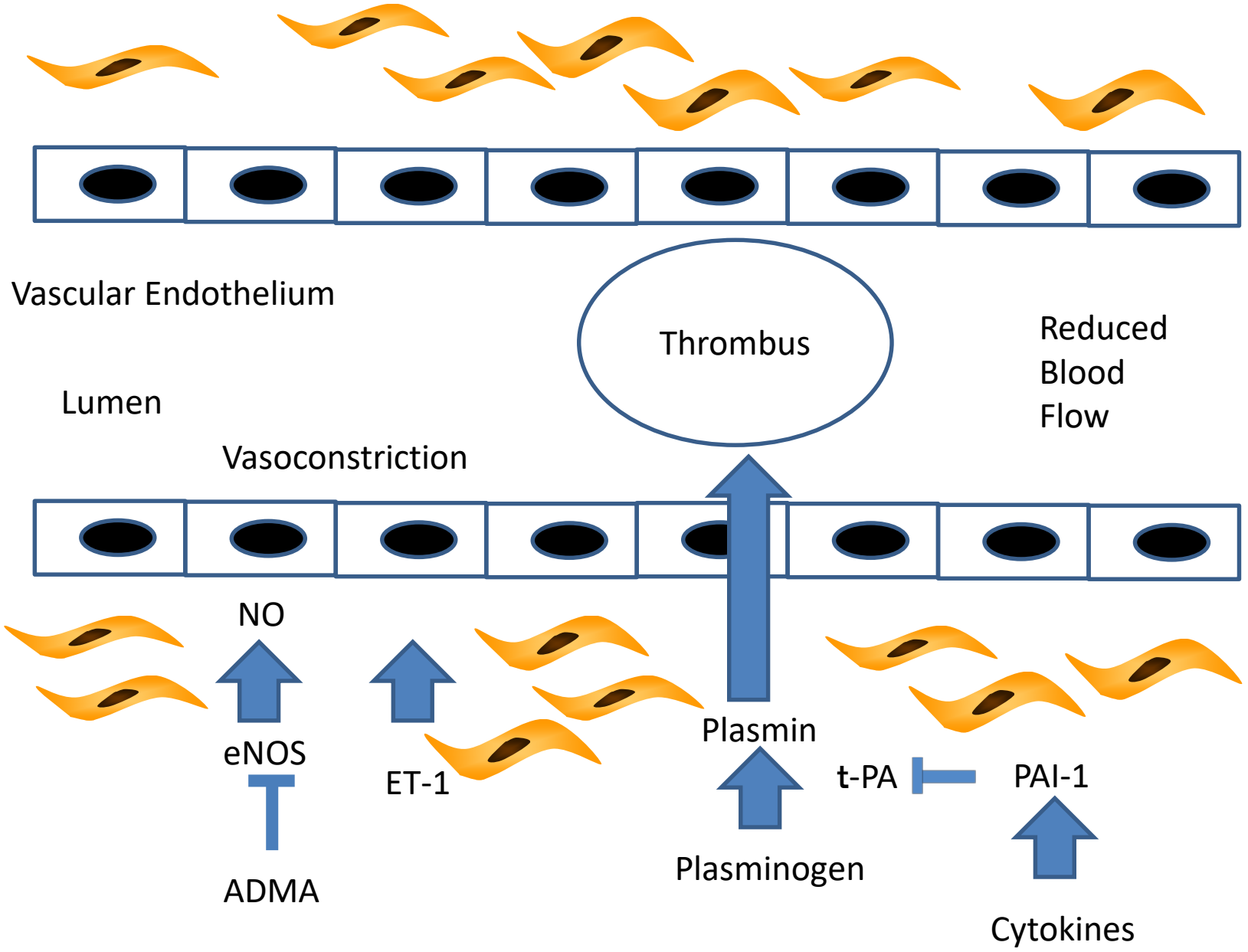
Category	Biomarkers
Lipids	apoA1, lipoprotein-associated phospholipase A_2, apoB100
Metabolism	adiponectin, leptin, insulin, ferritin, glucose. triiodothyronine
Blood coagulation and fibrinolysis	D-dimer, PAI-1
Angiogenesis	VEGF, placental growth factor
Renal function	creatinine, cystatin-C NGAL, N-acetyl-β-(D)-glucosaminidase β2-microglobulin urinary albumin-to-creatinine ratio
Myocardial injury	CK, creatine kinase MB fraction troponin I, troponin T myosin light-chain kinase I heart-type fatty acid binding protein heat shock protein 60 soluble TNF-related apoptosis-inducing ligand
Inflammation	CRP, TNF-α IL-1, IL-6, IL-10, IL-18 soluble TNF receptors 1 and 2 YKL-40 IL-1 receptor antagonist PTX3
Humoral factors	BNP, NT-proBNP, adrenomedulin, ANP
Neurohormones	norepinephrine renin angiotensin II aldosterone endothelin-1 thyroid hormones (FT3, FT4)
Oxidative stress	homocysteine, myeloperoxidase, VB_{12} oxidized LDLs urinary and plasma isoprostanes plasma malondialdehyde
Extracellular-matrix and remodeling	MMPs (MMP2, MMP3, MMP9), TIMP1 Collagen propeptides N-terminal collagen type III peptide Galectin-3

Abbreviations: apoA1, apolipoprotein A1; PAI-1, plasminogen activator inhibitor type-1; VEGF, vascular endothelial growth factor; NGAL, neutrophil gelatinase-associated lipocalin; CK, creatine kinase; TNF, tumor necrosis factor; CRP, C-reactive protein; IL, interleukin; YKL-40, chitinase-3-like-1 protein; PTX3, pentraxin 3; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; FT3, triiodothyronine; FT4, thyroxine; VB_{12}, vitamin B_{12}; LDL, low-density lipoprotein; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

Legend to Figure 1

Figure 1. Vascular injury and biomarkers.

At early stage of vascular injury the endothelium becomes dysfunctional. The elevation of asymmetric dimethylarginine (ADMA) leads to inhibition of endothelial nitric oxide (NO) synthase and decreased release of NO induces vasoconstriction. Endothelin-1 (ET-1) is released by dysfunctional endothelium. ET-1 also induces vasoconstriction and therefore reduces blood flow. Reduction of blood flow induces thrombotic tendency. Cytokine activation leads to the increase in the levels of plasminogen activator inhibitor type-1 (PAI-1). PAI-1 inhibits tissue-type plasminogen activator (t-PA) and diminishes fibrinolysis. Thus, ADMA, ET-1, NO, t-PA, and PAI-1 are potential biomarkers of vascular injury.



Fujii et al. Figure 1