ABSTRACT
Numerous studies have recently examined the role of pentraxin 3 (PTX3) in clinical situations. The pentraxin family includes Creactive protein (CRP); however, unlike CRP, PTX3 is expressed predominantly in atherosclerotic lesions that involve macrophages, neutrophils, dendritic cells, or smooth muscle cells. Interestingly, PTX3 gene expression in human endothelial cells is suppressed to a greater extent by pitavastatin than the expression of 6,000 other human genes that have been examined, suggesting that PTX3 may be a novel biomarker for inflammatory cardiovascular disease. The expression and involvement of PTX3 in cardiovascular diseases are discussed in this paper, along with the characteristics of PTX3 that make it a suitable biomarker; namely, that the physiological concentration is known and it is independent of other risk factors. The results discussed in this paper suggest that further investigations into the potential novel use of PTX3 as a biomarker for inflammatory cardiovascular disease should be undertaken.

KEYWORD: CRP, PTX3.

INTRODUCTION
In medicine, a biomarker is a measurable indicator of the severity or presence of some disease state. More generally a biomarker is anything that can be used as an indicator of a particular disease state or some other physiological state of an organism. A biomarker can be a substance that is introduced into an organism as a means to examine organ function or other
aspects of health. For example, rubidium chloride is used in isotopic labeling to evaluate perfusion of heart muscle. It can also be a substance whose detection indicates a particular disease state, for example, the presence of an antibody may indicate an infection. More specifically, a biomarker indicates a change in expression or state of a protein that correlates with the risk or progression of a disease, or with the susceptibility of the disease to a given treatment. Biomarkers can be characteristic biological properties or molecules that can be detected and measured in parts of the body like the blood or tissue. They may indicate either normal or diseased processes in the body.\[1\]

Basic research over the past decades has identified numerous candidate genes and proteins as biomarkers for cardiovascular disease. In the cardiovascular field, such biomarkers are useful not only for diagnosis but also as indicators of disease trait (risk factor or risk marker), disease state (preclinical or clinical), or disease rate (progression or prognosis).\[2\] One protein that has the potential to be a viable biomarker for inflammatory vascular disease is pentraxin 3 (PTX3).

2. PENTRAXIN 3

PTX3 is an evolutionarily conserved, multimeric acute phase inflammatory glycoprotein in the same family as the well-established cardiovascular biomarker C-reactive protein (CRP).\[^{3,4}\] PTX3 also shares 98% identity with tumor necrosis factor- (TNF-) stimulated gene 14 (TSG14).\[^{5,6}\] PTX3 has been successfully identified by Breviario et al. using differential screening of a cDNA library from human umbilical vein endothelial cells (HUVECs) stimulated by interleukin-1 beta,\[^{5}\] as well as by Gustin et al. using the 2D-DIGE approach to detect PTX3 in HUVECs stimulated by lysophospholipids.\[^{7}\] Our group also identified PTX3 when we were investigating statin as a target gene in HUVECs incubated with pitavastatin for 24 hours prior to RNA extraction.\[^{8}\] Interestingly, chip analysis has demonstrated that, of the 6,000 human genes that have been investigated for response to pitavastatin treatment, PTX3 gene expression is suppressed in human endothelial cells to the greatest extent. PTX3 synthesis is stimulated in endothelial cells, macrophages, myeloid cells, and dendritic cells by cytokines and endotoxins such as bacterial products, interleukin-1, and TNF.\[^{9-11}\] The role of PTX3 in neutrophils has also been gradually elucidated by a number of studies. Once synthesized, PTX3 is predominantly organized into covalent octamers through disulfide bonds.\[^{12}\] Although PTX3 is mainly localized in lactoferrin positive-specific granules,\[^{13-14}\] it is translocated to the surface of late apoptotic neutrophils
upon stimulation, where it accumulates in blebs and is rapidly released. PTX3 then binds with the high affinity complement component C1q to initiate the classical pathway of complement activation and facilitate pathogen recognition by macrophages.

2.1 Acute Coronary Syndrome (ACS)
The expression of PTX3 has been found to be increased in patients with acute myocardial infarction (AMI). For instance, Peri et al. observed that patients \((n = 37)\) with AMI who were admitted to the coronary care unit within 3.2 ± 3.2 hours of the onset of symptoms had increased plasma PTX3 over time.\(^{[15]}\) In this study, plasma PTX3 levels were found to peak at a median of 7.5 hours after AMI, and to return to normal levels after 3 days. Similarly, in murine models of AMI, PTX3 mRNA is expressed within 4 hours of the ligation of the coronary artery, reaches peak levels after 24 hours, and returns to normal levels 3 days later.\(^{[16]}\) We have also found that plasma PTX3 levels are increased in patients \((n = 16)\) with unstable angina pectoris (UAP; 6.20 ng/mL).\(^{[17-19]}\)

2.2 Congestive Heart Failure
PTX3 has also been implicated as a predictor of adverse clinical outcomes in patients with heart failure \((n = 196)\) in a study with a median follow-up period of 655 days and an ejection fraction of less than 50%.\(^{[20]}\) In a further study by Matsubara et al. that focused on patients with heart failure with normal ejection fraction (HFNEF), plasma PTX3 levels were also found to be increased \((3.26 (2.36–4.35) \text{ ng/mL})\). This was observed even in patients with HFNEF, although B-type natriuretic peptide (BNP) was within normal limits.\(^{[21]}\)

2.3 Heart Valvular Disease
In a study by Naito et al. that investigated PTX3 expression patterns in patients with aortic valve stenosis (AS) or regurgitation (AR), it was found that the expression of plasma PTX3 was significantly increased in patients with AS. Furthermore, PTX3 was found to be expressed predominantly in macrophage cells in the aortic valves of these patients.\(^{[22-23]}\)

4. CONCLUSION
Advances in genomics and proteomics technologies have led to the discovery of many novel biomarkers that provide valuable information, which can be used in disease screening and diagnosis, determining prognoses, and therapeutic monitoring. One potentially useful biomarker for cardiovascular disease is PTX3, and many studies have recently examined this protein in clinical situations. Although PTX3 is in the same protein family as CRP, it is
expressed predominantly in atherosclerotic lesions. Interestingly, the expression of PTX3 in endothelial cells has been shown in vitro to be suppressed to a greater extent by pitavastatin than other genes. We have therefore recently determined the normal physiological concentration of PTX3. As PTX3 has promise as a biomarker for cardiovascular disease, we have recently determined the normal physiological concentration of this protein. In addition, kits capable of detecting PTX3 are available, including a highly sensitive kit recently developed by our group, facilitating the use of PTX3 as a biomarker. Additional clinical study will be necessary to further elucidate the role of this protein in cardiovascular disease.

REFERENCES