Threshold Concept of Collagen Deposition as a Marker of Myocardial Interstitial Fibrosis in Atrial Fibrillation Cases

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ABSTRACT

Procollagen type I carboxyterminal propeptide (P1CP) and carboxy-terminal telopeptide of collagen type I (C1TP) were presented as peptides that reflect collagen synthesis and degradation and offer a much more helpful tool for detecting ECM alterations at a distance. In past years, clinical trials have been conducted to evaluate the use of these peptides as either prognostic or diagnostic biomarkers in patients with heart failure (HF). This study would investigate whether the combination of a collagen turnover marker and a collagen deposition marker is associated with different subtypes of atrial fibrillation (AF). As there is a new trend to investigate the roles of these markers in other cardiac diseases, this study would investigate whether the combination of the collagen turnover marker and the collagen deposition marker is associated with different subtypes of atrial fibrillation (AF).

Keywords: Atrial Fibrillations, Extracellular Matrix, Collagen Turnover

Introduction

Sinus node dysfunction (SND) is a series of problems affecting the sinus node and atrial impulse formation and diffusion that can be intrinsic, such as diseases [1], or extrinsic, such as medicines [2], and thus causes atrial fibrillation (AF), [3]. AF is an atrioventricular arrhythmia with variable R-R intervals, a lack of identifiable recurrent P waves, and variable atrial activation [4]. Older age, men sex, race, High blood pressure, previous atrial fibrillation, mitral valve disease, heart failure, LV hypertrophy, diastolic dysfunction, elevated LA volume, overweight, low body mass index, chronic obstructive pulmonary disease, long-lasting PR, diabetes, consumption of alcohol, tobacco use, and thyroid dysfunction are risk factors for atrial fibrillation (AF) [5]. As a result, the resulting Symptoms include heart palpitations, chest discomfort, shortness of breath, general weariness, and disorientation [6]. Hence, AF can be categorizedas paroxysmal, persistent, permanent, and Lone [7].

According to the data, extracellular matrix (ECM) abnormalities are evident in the principal forms of cardiac illnesses, such as basic myocardial disease and cardiomyopathy. Type I and III collagen is the most abundant structural protein in the myocardium, and its pro- or telopeptides are Secretion into the circulation throughout the progression of cardiovascular illnesses.Hence, these peptides may represent collagen synthesis and degradation. Patients with heart failure (HF) have been the subject of clinical investigations examining the use of these peptides as either prognostic or diagnostic biomarkers [8].

Collagen type I is a heterotrimeric molecule comprising two α-1 chains and one α-2 chain. During its synthesis, the protein undergoes a series of posttranslational changes to create the procollagen chain; this precursor is subsequently released into the extracellular environment and cleaved by particular proteinases [9]. C-terminal propeptide of type I procollagen (PICP; 100 kDa), secreted into the circulation, and collagen type I synthesized by cleavage have a 1:1 stoichiometric ratio [10].

PICP is secreted by the heart into the peripheral circulation via the coronary sinus [10]. However, whether there is, a significant association between plasma PICP and collagen levels in the myocardium remains uncertain. According to a cross-sectional investigation, plasma PICP levels in HCM patients were significantly associated with myocardium PICP content and the histological myocardial collagen volume percentage [11]. Similarly, Ferreira et al. confirmed that the serum levels of PICP were significantly elevated in hypertension before medication treatment [12].

PICP is a biomarker of type I collagen (COL1) production. During the extracellular conversion of pro-COL1 to COL1, serum pro-COL1 C-terminal propeptide is generated. The procollagen C-terminal proteinase enzyme triggers this reaction [13].

The C-terminal telopeptide of collagen type I (CITP; 12 kilodaltons) is a cross-linked terminal peptide secreted in a 1:1 stoichiometric ratio during the breakdown of collagen type I fibrils, allowing reliable assessment of collagen degradation [14, 15]. In a cross-sectional investigation, blood CITP levels were elevated in HCM patients, while PICP and PINP levels were unaffected, indicating a shift towards collagen type I degradation [16]. This is a significant finding, as collagen deposition is typically responsible for increased cardiac stiffness. However, many additional investigations have demonstrated that the association between CITP and myocardial fibrosis is contested. In patients with heart failure (HF) and atrial fibrillation (AF), serum CITP levels were considerably higher than in healthy controls [17, 18]. However, Nagao et al. found that serum CITP levels in individuals with DCM were not linked with left ventricular remodelling characteristics or the expression of heart collagen types I and III [19].

Moreover, several investigations have verified the prognostic significance of CITP. Plasma CITP was an independent prognostic factor of cardiovascular mortality in individuals with acute myocardial infarction, according to Manhenke et al. [20]. In this prospective analysis of 233 patients with AMI, 56% attained the composite endpoint of HF symptoms or CV mortality during the years of follow-up, and plasma CITP was elevated in patients who died from any cause. Similarly, serum CITP is beneficial for identifying cardiac events in individuals with heart failure (HF) [21]. In conclusion, CITP may improve the prognosis or diagnosis of myocardial fibrosis.

CITP is a marker for COL1 breakdown. Research indicates that CITP levels are elevated in the HFrEF and HFpEF patient categories. CITP serum levels are also higher in DCM and HCM patients. Klappacher et al. previously reported that serum CITP is significantly associated with myocardial collagen content. Kitahara et al. later concluded that CITP levels > 7.6 μg/L predict death [22]. Collagens can directly alter the wound microenvironment, serve as a scaffold for cell attachment and function, and supply biologically active principles or antimicrobials to promote wound healing [23].

Farhan Rizvi et al. (2020) recruited 90 patients without prior AF (56 patients with non-PoAF and 34 with PoAF) through the Aurora St. Luke's Medical Center to investigate the link between risk factors and baseline comorbidities between PoAF and non-PoAF patients. The protein biomarkers indicative of collagen turnover were evaluated in the preoperative blood samples of patients who developed POAF or stayed in SR. PICP, a biomarker of collagen I synthesis, had a trend towards greater levels that did not reach statistical significance, whereas CITP, a biomarker of collagen I degradation, did not differ substantially across groups [24].

Galdyszyn et al. (2023) hypothesized that the cells were obtained from the right atrium of patients suffering from aortal stenosis undergoing an operation. Individual atrial fibroblasts and myofibroblasts were grown on soft and rigid polyacrylamide gels. Positively stained cells were determined to be fibroblasts or myofibroblasts. The cultures settled on stiff gel had reduced intra-cellular collagen and collagen type I telopeptide (PICP) levels measured in the culture media; P1CP content reflects collagen synthesis; a higher PICP concentration was observed in cells cultured on the soft substrate compared to those cultured on the stiff substrate; this contributed significantly to the regulation of fibrosis [25].

There have been two types of fibrosis noted: interstitial and replacement. The buildup of collagen between cardiomyocytes characterizes interstitial fibrosis; excessive collagen deposition within the atria raises the risk of atrial fibrillation (AF); and on the stiff substrate, atrial fibroblast and myofibroblast cells accumulate less collagen than those on the soft substrate. This effect shows that physical environmental stressors influence atrial fibrosis; however, no similar effect was detected on procollagen types I and III expression. In cultures grown on the rigid substrate, procollagen type I carboxyterminal propeptide (PICP) levels were lower, indicating decreased type I collagen synthesis [25]

KOBAYASHI et al. (2022) reported the association among collagen synthesis markers and different echocardiographic variables: elevated serum PICP was positively associated with heart structural as well as functional defects (left ventricular hypertrophy, left atrial enlargement, and significantly larger ventricular stiffness), while lower serum PICP was significantly associated with cardiac structural and functional abnormalities. In patients treated with spironolactone, a decrease in serum PICP was associated with improved diastolic dysfunction, as measured by E/e′. These data support PICP as the marker of choice for assessing cardiac fibrosis and response to spironolactone; reductions in serum PICP with therapy are linked with decreased fibrosis in endomyocardial biopsies in both non-HF and HF patients [26].

Boyalla et al. (2022**)** also did a meta-analysis that found 73 studies and 14,148 participants that explored baseline biomarkers and their connection with AF recurrence following CA after applying inclusion and exclusion criteria. The principal findings of this meta-analysis in patients receiving CA indicate that high-sensitivity carboxy-terminal telopeptide of collagen type I (C1TP) is substantially linked with identifying individuals with AF recurrence as compared to the non-recurrence group and The levels of lipid profile markers (cholesterol, LDL, HDL, and TG) did not differ between the groups (recurrence versus non-recurrence) after AF ablation [27]. In a recent meta-analysis, however, the incidence of arrhythmia recurrence was decreased by less than 55% in CA compared to medical therapy [28].

Ravassa combined fibrosis markers (including CITP) in a recent study, suggesting that the cross-linking and accumulation involved in left atrial electrical remodelling independently predict recurrence after CA. This is the first meta-analysis to demonstrate the pooled effects of CITP and its correlation with AF ablation outcomes [29].

The Implication and Contribution To the Knowledge gap

Even though nothing was known about circulating biomarkers of collagen metabolism, it was shown that P1CP and C1TP are important in preventing long-term damage to cardiac muscle. Both markers were utilized to identify the severity of fibrosis. Because collagen turnover was associated with numerous disorders, including hypertrophic cardiomyopathy (HCM) [30], hypertensive heart disease (HHD) [31], dilated cardiomyopathy (DCM) patients [32], acute myocardial infarction (AMI) [33], and heart failure (HF) with diastolic dysfunction [34, 35].

Several significant limitations hinder its clinical utility. A future study must demonstrate the relationship between the observed levels of these biomarkers, the myocardial collagen network, and the variations in heart structure and function. In addition, it may be prudent to

perform a prospective validation of the incremental information provided by a multi-marker strategy combining these peptides with standard biochemical markers such as natriuretic peptides or troponins, as well as an evaluation of the effects of their measurements on patient management and outcomes.

List of abbreviation

HFpEF: Heart Failure with Preserved Ejection Fraction.
HFrEF: Heart Failure with Reduced Ejection Fraction.
C1TP: Carboxy-Terminal Telopeptide of Collagen Type I.
P1CP: Carboxy-Terminal Propeptide of Procollagen Type I.
COL1: Collagen Type I.
ECM: Extracellular Matrix.
HCM: Hypertrophic Cardiomyopathy.
DCM: Dilated Cardiomyopathy.
SND: Sinus Node Dysfunction.
AMI: Acute Myocardial Infarction.
PoAF: Postoperative Atrial Fibrillation.
HDL: High-Density Lipoprotein.
LDL: Low-Density Lipoprotein.
HF: Heart Failure.
AF: Atrial Fibrillation.
LV: Left Ventricular.
LA: Left Atrial.
CA: Coronary Artery.
SR: Sinus Rhythm
TG: Triglycerides.
PR: Prolonged.
KDa: Kilo Dalton.
E/e′: Early diastolic transmitral flow velocity/early diastolic mitral annular velocity.

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