SERUM BIOMARKERS OF COLLAGEN TYPE I AND TYPE III TURNOVER IN HEART FAILURE – THE NEED FOR REAPPRAISAL

ASPARUH NIKOLOV[1], MARIA TZEKOVA[2] and KONSTANTIN KOSTOV[2]

[1]Cardiovascular Research Working Group, Institute for Scientific Research, Medical University of Pleven, Pleven and [2]University Hospital Pleven, Second Clinic of Cardiology, Department of Propaedeutics in Internal Medicine, Medical University of Pleven, Pleven, Bulgaria

Cardiac extracellular matrix is a complex structure presented by a network of fibrillar collagen, fibronectin, laminin, fibrillin, elastin, glycoproteins and proteoglycans. Myocardial fibrillar collagens (collagen type I and type III) are the main proteins responsible for the structural integrity of the bordering cardiomyocytes. Increased accumulation of fibrillar collagen leading to fibrosis has been reported in pathological cardiovascular conditions like heart failure. Amino-terminal and carboxy-terminal propeptides of collagen type I and III are the two major collagen types playing a central role in this process. Derived products from their turnover have been determined in serum of patients with heart failure. Collagen type I and III propeptides reflect collagen synthesis and degradation. Their use as biomarkers with prognostic or diagnostic aim is an area of intensive studies. This review article summarizes the actual available literature data on serum markers of collagen type I and III turnover in heart failure and discusses their potential as circulating indicators of cardiac fibrosis. The use of collagen type I and III peptides for diagnosis, prognosis and monitoring of heart failure is thoroughly discussed too.

Key words: collagen, biomarkers, heart failure, myocardial fibrosis

Address for correspondence: Assoc. Prof. Asparuh Nikolov
Cardiovascular Research Working Group
Institute for Scientific Research
Medical University
1, St. Kliment Ohridski Str.
5800 Pleven, Bulgaria
Tel. ++359 887100672
E-mail: a_nicoloff@yahoo.com

HEART FAILURE

Heart failure (HF) is a global health problem that affects about 40 million people worldwide (1). Approximately 2% of adults have HF and in those over the age of 65, it increases to 6%-10% (2). Above 75 years of age, the rates are greater than 10% (3). Unfortunately, morbidity rate is predicted to increase because of the increased life span and risk factors such as hypertension, diabetes, dyslipidemia, and obesity (4). HF is the leading cause of hospitalization in people older than 65.

The main terminology used to describe HF is historical and based on measurement of the left ventricular ejection fraction (LVEF). HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as 40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40%-49% represent a 'grey area', which the European Society of Cardiology (ESC) now defines as HFmrEF. Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, comorbidities and response to therapies (5).

EXTRACELLULAR MATRIX ABNORMAL CHANGES IN HEART FAILURE

Extracellular matrix (ECM) includes a network of fibrillar collagen, basement membrane and proteoglycans. Fibrillar collagens (collagen type I and type III) ensure structural integrity of the boundary cells,

thus ensuring structural stability. ECM is a dynamic, metabolically active structure that plays an independent and important role in the progression of multiple vascular diseases. Increased accumulation of fibrillar collagen, or fibrosis, has been observed in various pathological conditions. Heart failure is a well-known example of such an adverse accumulation of ECM, raising myocardial stiffness and impairing heart contractile behavior. According to the current knowledge, the most certain collagen type I and III turnover biomarkers with clinical and laboratory value are the following four: N-terminal propeptide of collagen type I (PINP), N- terminal propeptide of collagen type III (PIIINP), C-terminal propeptide of collagen type I (PICP) and C-terminal telopeptide of collagen type I (ICTP). All of them are collagen-derived peptides as PINP and PICP reflect collagen type I synthesis, PIIINP reflects collagen type III synthesis, while ICTP shows collagen type I degradation.

It is well known that some cardiovascular diseases such as hypertension, coronary artery disease, valvular disease, and arrhythmias often progresses to HF. An association between cardiac remodeling and development of HF has been estimated (6). Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes that manifest clinically as alterations in the size, mass, geometry and function of the heart after a stressful stimulus. This process can be triggered by ischemia (myocardial infarction) (7,8), inflammation (myocarditis), hemodynamic overload (workload by volume or pressure) (9) and neurohormonal activation (10,11). Cardiac remodeling is considered to be not only an adaptive event but also a maladaptive process. In result, at first stage cellular changes occur in heart structure such as myocyte hypertrophy, necrosis, apoptosis, followed by second stage of an increased ECM deposition of fibrillar collagen, often described by the term 'myocardial fibrosis'. It is associated with accelerated collagen metabolism and impaired synthesis and accumulation mainly of collagen type I and III in myocardium (12-18). In later stages of remodeling, heart function is inevitably impaired.

COLLAGEN TYPE I CHARACTERISTICS

Type I collagen is a fibrillar collagen and a major part of the interstitial membrane structure. It is the most prevalent type of collagen and a key structural composition of many tissues. It is found practically in all structures involving connective tissue. Type I collagen is the main structural protein of bone, skin, tendon, ligaments, sclera, cornea, blood vessels, as well as an important component of other tissues. It is collected in fibers forming structural-mechanical scaffold (matrix) of bones, skin, tendons, cornea, blood vessel walls, and other connective tissues. Heterotrimers of two α1 (I) and one α2 (I) chains are the dominant isoform of type I collagen. Homotrimers of three α1 (I) chains are found in fetal tissues and some fibrous lesions (19). The homotrimeric isoform is more resistant to cleavage than collagenases, which may explain its accumulation and functional role in tumors and fibrotic lesions (Fig. 1).

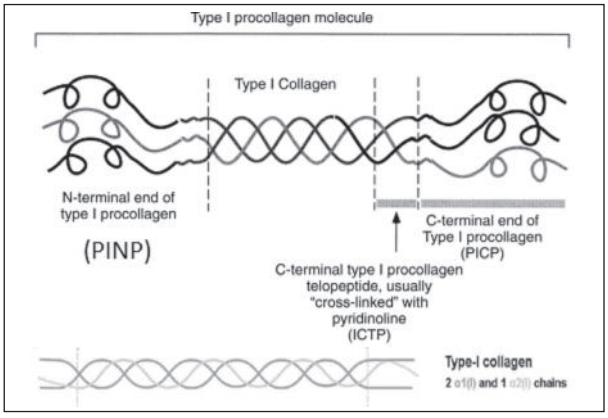

Fig. 1. *Collagen type I structure*

PICP = collagen-derived peptide including the carboxy-terminal peptide of procollagen type I formed on extracellular conversion of procollagen type I into fibrillar collagen I; PINP = collagen-derived peptide including the amino-terminal propeptide of collagen type I; ICTP = telopeptide of collagen type I. Adapted from Gao L, Orth P, Cucchiarini, M, Madry H. Effects of solid acellular type-I/III collagen biomaterials on in vitro and in vivo chondrogenesis of mesenchimal stem cells. Exp Rev Med Devices 2017; 14(9):717-32.

COLLAGEN TYPE III CHARACTERISTICS

Type III collagen is composed of one collagen α-chain, unlike most other collagens. It is a homotrimer containing three α1 (III) chains overlapped in a right triple helix. Type III collagen is secreted by fibroblasts and other types of mesenchymal cells, thus playing a major role in different inflammatory pathological conditions such as lung damage, liver diseases, renal fibrosis, and vascular fibrosis. Both collagen type III and type I are the main components of the ECM (20). Type III collagen immunological biomarkers have been developed and widely used for detection of fibrosis (Fig. 2).

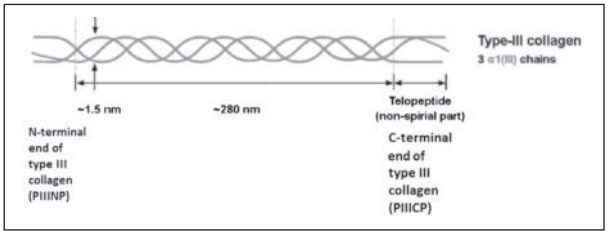

Fig. 2. *Collagen type III structure*

PIIINP = collagen-derived peptide including the amino-terminal propeptide of collagen type III arising on extracellular conversion of procollagen III to fibrillar collagen III to fibrillar collagen III. Adapted from Gao L, Orth P, Cucchiarini M, Madry H. Effects of solid acellular type-I/III collagen biomaterials on in vitro and in vivo chondrogenesis of mesenchimal stem cdells. Exp Rev Med Devices 2017; 14(9) 717-32.

CARDIAC FIBROSIS

Extracellular matrix is composed of fibrillar collagen types I and III, fibronectin, laminin, fibrillin, elastin, glycoproteins and proteoglycans; cardiac fibroblasts are the primary source of these ECM proteins. Cardiac fibroblasts also produce matrix metalloproteinases (MMPs), as well as tissue inhibitors of MMPs (TIMPs), which are ECM-regulatory proteins. MMPs are proteases that degrade ECM proteins and TIMPs can inhibit MMP function; their balanced equilibrium is critical for ECM homeostasis.

Cardiac ECM is composed predominantly of collagen type I (85%) and III (11%). Collagen type I and III are synthesized by cardiac fibroblasts. They are the main collagen-producing cells in the heart. Fibrillar collagen is synthesized firstly as a procollagen, which is split by specific proteinases in carboxy (C)- and amino (N)-terminal propeptides.

The N-terminal propeptides of collagen type I or III (PINP and PIIINP) and the C-terminal propeptides (PICP and PIIICP) are used as markers of collagen type I or III synthesis. After splitting of the propeptides, the triple helix chain will form big collagen fibers with other collagen chains. During degradation of these collagen fibers by collagenases (MMP-1, -8, -13), telopeptides are formed. The big telopeptide undergoes spontaneous denaturation in nonhelical derivatives, which are completely degraded into inactive fragments by interstitial gelatinases (MMP-2, -9). The small telopeptide of collagen type I (ICTP, 12 kDa) can be used as a marker of collagen type I degradation (21).

Accumulation of fibrillar collagen, or fibrosis, is intensified in heart failure. Early studies in the field of congestive heart failure (CHF) clearly demonstrate that extracellular degradation enzymes (MMPs) are found in the myocardium of patients with CHF (22). Evaluation of cardiac collagen metabolism by biological markers is a useful tool for monitoring cardiac tissue remodeling and fibrosis, both in laboratory models and in clinical studies (23). Along with increasing levels of collagen synthesis markers, the results reported from some studies suggest that collagen degradation is slower in patients with CHF, leading to cardiac fibrosis (19,20).

Fibrosis is a response of hyperactivity of cardiac fibroblasts that occurs in response to certain stressful stimuli. As a result, recruitment and proliferation of circulating bone marrow-derived cells infiltrate the myocardium and transform into cardiac fibroblasts. It has been reported in some studies that increased levels of collagen synthesis biomarkers (PICP, PINP, PIINCP, PIIINP) and reduced serum levels of collagen type I degradation biomarker (CITP) lead to collagen deposition and fibrosis (24-26). These data show that the balance between cardiac collagen synthesis and degradation is disturbed in pathogenic conditions (22,23). Patients with heart failure are an example of impaired collagen turnover (27,28).

CIRCULATING SERUM COLLAGEN BIOMARKERS AND HEART FAILURE

Several studies have been performed on collagen type I and III metabolism so far. They show that their turnover is mainly regulated by N-terminal propeptide of collagen type I (PINP), N- terminal propeptide of collagen type III (PIIINP), C- terminal propeptide of collagen type I (PICP) and C-terminal telopeptide of collagen type I (ICTP). They are collagen-derived peptides as PINP and PICP show collagen type I synthesis, PIIINP reflects collagen type III synthesis, while ICTP marks collagen type I degradation (25,26).

N-terminal propeptide of collagen type III (PIIINP)

PIIINP is a marker of collagen type III synthesis. Most serum PIIINP is generated during the extracellular conversion of procollagen type III to collagen type III by the enzyme procollagen aminoterminal proteinase (29). Serum PIIINP concentration correlates with the myocardial area fractions of their tissue analogs. The increase in ECM turnover, which may partially be derived from fibrosis in the myocardium, can be measured in the serum of patients with dilated cardiomyopathy, and has an impact on risk stratification and prognosis (30). In addition, reduction in the extent of collagen volume fraction in HF patients treated with spironolactone is accompanied by reductions in serum PIIINP (31) Serum PIIINP is associated with the severity (43) and outcomes of HF of different causes regardless of EF (32,33).

PIIINP levels are elevated in all HF patients regardless of EF. There is a decreased survival rate in patients with HFrEF, but the cutoff point is different, i.e. according to Zannad *et al.* (33) PIIINP >3.85 **μg**/L, in comparison with data of Klappacher *et al.* (30) PIIINP >7 **μg**/L, with clarification that patients in the latter study were all with dilated cardiomyopathy (33 idiopathic and 8 ischemic cases). Patients with HF, dilated and hypertrophic cardiomyopathy (DCM, HCM) have significantly higher serum PIIINP levels than healthy control subjects. Hypertensive patients with HFpEF also have significantly higher serum PIIINP concentrations than hypertensive patients with HFrEF and HFmrEF (31). The survival rate decreases if the

patient with HF (33,35) or with DCM (36) has an elevated PIIINP level. The serum PIIINP concentration is also significantly higher in patients with acute myocardial infarction and PIIINP >5 μg/L is an independent predictor of cardiac death and in-hospital development of CHF (37). There is only one study with patients with HFmrEF (32) which reports a decreased survival if PIIINP >4.7 μg/L (Table 1).

Table 1.
Serum levels of PIIINP in patients with heart failure

Author	Heart failure type	Main findings
Alla *et al.* (23)	HFrEF	Increased PIIINP levels
Barasch *et al.* (57)	HFrEF vs. HFpEF	Associated with HFpEF
Cicoira *et al.* (35)	HFmrEF	Decreased survival if PIIINP >4.7 **μg**/L
Martos *et al.* (34)	HFpEF	Increased PIIINP levels
Plaksej *et al.* (50)	HF	Increased levels in NYHA III + IV class
Zannad *et al.* (33)	HFrEF	Decreased survival if PIIINP >3.85 **μg**/L
Zile *et al.* (64)	HF	Increased PIIINP levels
Klappacher *et al.* (30)	DCM	Decreased survival if PIIINP >7 **μg**/L
Host *et al.* (37)	HF	Increased PIIINP levels
Schwartzkopff *et al.*(65)	HF	Independent predictors of mortality
Michalski *et al.* (67)	HFrEF *vs.* HFpEF	PIIINP showed strong negative correlation with LV-strains
MESA (Multi-Ethnic Study of Atherosclerosis) (67)	HF	Increased PIIINP levels

NYHA = New York Heart Association; DCM = dilated cardiomyopathy; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

N-terminal propeptide of collagen type I (PINP)

PINP is a marker of collagen type I synthesis. Procollagen type I propeptides are derived from collagen type I. This precursor contains a short signal sequence and terminal extension peptides, amino-terminal propeptide (PINP) and carboxy-terminal propeptide (PICP). These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I (38,39). In comparison with control subjects, PINP is not significantly different in patients with HCM (40), HF (41) and in hypertensive patients with or without diastolic HF (34).

C-terminal propeptide of collagen type I (PICP)

PICP is a marker of collagen type I synthesis. Serum carboxy-terminal propeptide of procollagen type I (PICP) is generated during the extracellular conversion of procollagen type I into collagen type I by the enzyme bone morphogenetic protein-1 or procollagen carboxy-terminal proteinase (42). A net release from heart into the circulation has been reported in HF (43), suggesting a cardiac origin of systemic PICP. Serum PICP concentrations correlate with collagen volume fraction (43-45) in HF. Results reported by of Lopez *et al.* (45) show that PICP levels decrease in patients with hypertensive heart failure with torasemide treatment. Serum PICP is associated with HFrEF severity (46), and with mortality in HFpEF (47) and HFrEF (48). Of interest, the serum PICP-to-serum PIIINP ratio is related to malignant ventricular arrhythmogenesis in HF (49). Data show that PICP levels are significantly increased in more studies with patients with HFpEF than HFrEF. Higher serum PICP level is found in patients with HF compared to control subjects, except for the studies by Alla *et al*. (22) and Plaksej *et al*. (50). Serum PICP, as well as coronary PICP, is positively correlated with the myocardial collagen content (51,52). There is no difference in serum PICP levels in patients with HCM (53) and DCM (54) as compared to controls. There is only one study including patients with HFmrEF, which shows that an excess of cardiac collagen type I synthesis and deposition may be involved in the enhancement of myocardial fibrosis that accompanies development of HF in hypertensive heart disease (43) (Table 2).

Table 2.
Serum levels of PICP in patients with heart failure

Author	Heart failure type	Main findings
Gonzalez *et al.* (45)	HFpEF	Increased PICP levels in both groups, patients with NYHA class II to IV CHF treated with torasemide *vs.* furosemide
Querejeta *et al.* (43)	HFmrEF	Increased PICP levels
Plaksej *et al.* (50)	HF	Non significant difference
Lopez *et al.* (51)	HHD	Strong correlation between myocardial collagen content and serum concentration of PICP
Martos *et al.* (34)	HFpEF	Increased PICP levels
Barasch *et al.* (57)	HF	Associated with HFpEF
Alla *et al.* (23)	HFrEF	Nonsignificant difference
Schwartzkopff *et al.*(65)	HFmrEF	Nonsignificant difference

NYHA = New York Heart Association; HHD = hypertensive heart disease; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

C-terminal telopeptide of collagen type I (ICTP)

ICTP is a marker of collagen type I degradation. Data show that ICTP levels are elevated in both groups, HFrEF and HFpEF. Increased ICTP serum levels are observed in patients with DCM and HCM too. Serum ICTP is positively related with collagen content in the myocardium (30) and it is a predictor of mortality if >7.6 μg/L (55). In hypertensive patients with HF, serum ICTP level is increased in NYHA class IV (50). Barasch *et al*. (56) did not find an association between ICTP and HFrEF and HFpEF. In patients with acute myocardial infarction, Manhenke *et al*. (57) demonstrated that ICTP was an independent predictor of total and cardiovascular mortality.

Serum collagen type I telopeptide-to-serum matrix metalloproteinase-1 ratio is a novel candidate marker studied in the last two years. As collagen cross-linking determines collagen fiber resistance to MMP degradation, the higher the cross-linking of collagen type I fibers, the lower is the cleavage of the peptide collagen type I telopeptide (CITP) by the enzyme MMP-1. Thus, the serum CITP-to-serum MMP-1 ratio is inversely correlated with myocardial collagen cross-linking (58). The CITP-to-MMP-1 ratio is independently associated with the risk of HF hospitalization (58). The combination of low CITP-to-MMP-1 ratio and high PICP identifies HF patients with the highest risk (59) (Table 3).

Table 3.
Serum levels of ICTP in patients with heart failure

Author	Heart failure type	Main findings
Plaksej *et al.* (50)	HF	Increased ICTP levels in NYHA IV
Kitahara *et al.* (55)	HFpEF	Event-free point decreases when ICTP >7.3 ng/mL
Barasch *et al.* (57)	HF	Not associated with HFpEF or HFrEF
Zile *et al.* (64)	HFpEF	Increased ICTP levels
Klappacher *et al.* (30)	DCM	Increased mortality if ICTP >7.6 μg/L
Schwartzkopff *et al.* (65)	HFmrEF	Increased ICTP levels
Batlle *et al.* (68)	HF	Increased ICTP levels and increased risk of clinical event
MESA (Multi-Ethnic Study of Atherosclerosis) (67)	HF	High levels of circulating ICTP

NYHA = New York Heart Association; DCM = dilated cardiomyopathy; HF = heart failure not defined by left ventricular ejection fraction (LVEF); HFrEF = heart failure with reduced ejection fraction (LVEF <40%); HFmrEF = heart failure with mid-range ejection fraction (LVEF 40%-49%); HFpEF = heart failure with preserved ejection fraction; (LVEF ≥50%)

CONCLUSIONS AND PERSPECTIVES

Alteration of ECM structure and function may be the key in revealing the mechanism of cardiac remodeling. Impairment of the ECM network integrity disorganizes and interrupts connections between myocardial cells and blood vessels. This could later lead to shifting of heart function. Fibrosis and overproduction of ECM proteins result in enhanced stiffness of the myocardium wall, followed by systolic and diastolic dysfunction.

The use of serum collagen-derived peptides (PINP, PICP, PIIINP and ICTP) for collagen type I and III turnover in heart failure is very promising. Potential routine clinical applications of serologic markers of collagen metabolism can hopefully be introduced soon. Despite this fact, there are some controversial findings and limitations in the studies commented here. Some important critical remarks make gaps in evidence. That is why the following questions concerning PINP, PICP, PIIINP and ICTP as indicators for diagnosis, prognosis and development of heart failure should to be taken into account:

- Changes in collagen turnover are likely to occur at a very early stage of heart failure, even before disease is clinically diagnosed. Can collagen biomarkers be used to predict development and prognosis of heart failure?
- Whether collagen metabolism markers give enough information as lone indicators, or do we need a combination model adding other cardiovascular markers, for example creatine phosphokinase, troponin? Furthermore, is it more appropriate to use an integrative model using combination of serum markers and image test than using just one of them for diagnosis, prognosis and monitoring of heart failure?
- Analyzing the above mentioned studies, some differences can be noted between the cutoff points for detection of serum levels of collagen turnover markers in HF according to the EF.
- In hypertensive patients with heart failure, serum collagen type I telopeptide-to-serum matrix metalloproteinase-1 ratio (ICTP/MMP-1) is independently associated with the risk of HF hospitalization (58). The combination of low CITP-to-MMP-1 ratio and high PICP identify HF patients with the highest risk than ICTP alone (59). Not only their absolute serum levels, but also the relationship between their serum concentration ratios could play a role in myocardial remodeling in HF. Probably the ratios between collagen marker and MMP are a more accurate indicator than a marker alone.
- The underlying factor causing the heart failure syndrome affects collagen biomarker turnover in different ways. For example, hypertension is ac-

companied by hypertrophy of cardiac myocytes and increased stiffness of the ventricle wall, which suggests an increase in collagen fibers. Patients with hypertension have thus an increase in biomarkers of the synthesis of collagen, such as PII-INP and PICP.

- Different characteristics of HF patients such as HF treatment, comorbidities, age and body mass index can influence the levels of collagen biomarkers.
- Cardiac remodeling is a continuous process, while most studies were cross-sectional and report the levels of biomarkers only at one certain time point. These biomarkers should, however, be determined at various time points of the remodeling process. There is a need for larger and longitudinal investigations.
- Is a serum biomarker representative of the tissue level? A method to correlate serum levels of the biomarkers with cardiac remodeling is immunohistochemistry and histology of cardiac biopsies, which cannot be performed in cross-sectional studies. In some studies, the association between serum biomarkers and collagen content in the myocardium was investigated and serum PICP concentration was directly correlated with the fibrillar collagen fraction of the myocardium (43,52), which suggests that PICP is representative for cardiac collagen. PIIINP is also correlated with collagen type III and collagen type I, which makes PIIINP less representative for collagen type III synthesis alone (32).
- The propeptides can be incorporated in the network of collagen fibers and not cleaved off and eliminated in the circulation. At this point, PINP and PIINP underestimate partially collagen synthesis. The elimination of the peptides occurs through various pathways and is a variable process, which can affect the concentration of the biomarkers (60,61).
- Testing for circulating biomarkers of myocardial interstitial fibrosis presents several limitations. They are not thoroughly cardiac-specific, and changes in their concentrations may represent integrated abnormalities of the cardiovascular collagen and/or influence of comorbidities affecting collagen metabolism. Fibrosis also occurs in other organs and it is possible that increased levels of these biomarkers come not only from cardiac origin but also from other diseased organs such as bone, liver, kidneys and lungs. That is why in all reported studies osteoporosis, renal failure and hepatic fibrosis were used as exclusion criteria (62).
- In most of the studies, patients were obviously treated with standard HF pharmacotherapy. However, does the drug treatment affect the elimination of these propeptides by liver and kidneys and does it interfere with the dynamic processes in cardiac extracellular matrix?

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SAŽETAK

SERUMSKI BIOMARKERI PRETVORBE KOLAGENA I I III. KOD ZATAJENJA SRCA – POTREBA PONOVNE PROCJENE

A. NIKOLOV[1], M. TZEKOVA[2] i K. KOSTOV[2]

[1]Radna skupina za istraživanje srčanožilnih bolesti, Zavod za znanstveno istraživanje, Medicinski fakultet u Plevenu, Pleven i [2]Sveučilišna bolnica Pleven, Druga kardiološka klinika, Odjel propedeutike u internoj medicini, Medicinski fakultet u Plevenu, Pleven, Bugarska

Ekstracelularni matriks srca je složena struktura koja se prikazuje kao mreža vlaknatog kolagena, fibronektina, laminina, fibrilina, elastina, glikoproteina i proteoglikana. Vlaknati kolageni miokarda (kolagen tipa I. i tipa III.) su glavni proteini o kojima ovisi strukturni integritet graničnih kardiomiocita. Povećano nakupljanje vlaknatih kolagena koje dovodi do fibroze opisano je u patološkim kardiovaskularnim stanjima kao što je zatajenje srca. Amino-terminalni i karboksi-terminalni propeptidi kolagena tipa I. i III. dva su glavna tipa kolagena koji imaju središnju ulogu u tom procesu. Produkti njihove pretvorbe određivani su u serumu bolesnika sa zatajenjem srca. Propetidi kolagena tipa I. i III. odražavaju sintezu i raspad kolagena. Njihova upotreba kao biomarkera područje je intenzivnih studija sa svrhom prognoze ili dijagnoze. Ovaj pregledni rad sažima danas raspoložive podatke iz literature o biljezima pretvorbe kolagena tipa I. i III. kod zatajenja srca i raspravlja se o njihovom potencijalu kao cirkulirajućim pokazateljima fibroze srca. Raspravlja se i o primjeni peptida kolagena tipa I. i III. za dijagnozu, prognozu i praćenje zatajenja srca.

Ključne riječi: **kolagen, biomarkeri, zatajenje srca, fibroza miokarda**