iterations of the structure and composition of cardiomyocyte and noncardiomyocyte compartments of the myocardium appear to play a central role in the pathogenesis of heart failure (HF) associated with a number of cardiac diseases. Among these alterations, changes in the quantity and quality of the extracellular matrix, including the collagen network, have been characterized that induce remodeling of the myocardium and ultimately deteriorate left ventricular (LV) function and facilitate the development of HF. Studies on circulating biomarkers of collagen metabolism have attracted the attention of the medical community, and some circulating biomarkers have been proposed as potential useful tools to improve diagnosis, prognosis, and therapy in cardiac diseases that develop HF. However, the available data are far from conclusive and from affording incremental value to the knowledge provided by more classic diagnostic tools. This is due mainly to 3 limitations. First, collagen is the most abundant protein in the body, and its turnover is so dynamic that not all circulating molecules proposed as biomarkers actually reflect changes in collagen metabolism, namely at the cardiac level. Second, a thorough understanding of the association of a given biomarker with the pathological features of the collagen network in the cardiac disease under study has not been considered essential, thus weakening its pathophysiological meaning. Third, several methodological issues may introduce a number of confounding factors into the measurements of circulating biomarkers of collagen metabolism, thus bringing into question the validity of the available results. Therefore, this article is not aimed at providing a systematic review of all the published information on circulating biomarkers of collagen metabolism in cardiac diseases but at analyzing the biochemical, pathophysiological, and methodological aspects to be taken into account to overcome the above limitations and to improve the clinical applicability of such molecules.

Circulating Biomarkers of Collagen Metabolism

Collagen Metabolism

The extracellular matrix contains a fibrillar collagen network, a basement membrane, proteoglycans and glycosaminoglycans, and bioactive signaling molecules. The collagen network is a metabolically active structure in the sense that the balance between the synthesis and degradation of collagen determines its turnover, which is estimated to be from 80 to 120 days. The turnover is regulated by fibroblasts and by fibroblasts differentiated to myofibroblasts (Figure 1). These cells respond to mechanical stretch, autocrine and paracrine factors generated locally (eg, vasoactive peptides such as angiotensin II and growth factors such as transforming growth factor-β or connective tissue growth factor), and hormones derived from the circulation (eg, aldosterone). In addition, a number of proinflammatory cytokines (eg, tumor necrosis factor-α, interleukin-1 and -6) secreted by monocytes and macrophages also influence the function of fibroblasts and myofibroblasts. The responses of these cells to all the aforementioned factors include changes in their rates of proliferation and migration and modifications in their capacity to synthesize and secrete fibrillar collagen precursors (namely the 2 more abundant subtypes present in the heart: procollagen types I and III), as well as enzymes that process procollagen precursors to mature collagen able to form fibrils and fibers (eg, procollagen proteinases and lysyl oxidase), enzymes that degrade collagen molecules within fibers (eg, matrix metalloproteinases [MMPs]), and signaling molecules that regulate the interaction of the extracellular matrix with parenchymal cells (eg, matrix metalloproteinases) (Figure 1). The clinical investigation of circulating biomarkers of collagen metabolism has provided a number of candidate molecules that can be classified into 2 categories: biomarkers related to the synthesis of collagen molecules that will form the new collagen fibers and biomarkers related to the degradation of collagen molecules integrating the old fibers.

Biomarkers Related to Collagen Synthesis

Once procollagen types I and III are synthesized and secreted by fibroblasts and myofibroblasts as a triple-helix procollagen precursor containing terminal propeptides, the propeptides are cleaved in block by specific procollagen proteinases, allowing the integration of the resulting collagen molecule into the growing fibril. The released propeptides reach the bloodstream and can be detected in blood. If the propeptides are cleaved in every molecule of collagen and the amount of

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propeptides quantified in the circulation is proportional to the amount of collagen formed, these propeptides qualify as indexes of collagen synthesis. This holds true for the carboxy-terminal propeptide of procollagen type I (PICP) and likely for the amino-terminal propeptide of procollagen type I (PINP) (Figure 2). In fact, a stoichiometric ratio of 1:1 exists between the number of collagen type I molecules produced and the PICP molecules released. On the other hand, the carboxy-terminal and amino-terminal propeptides of collagen type III (PIIICP and PIIINP, respectively) are not completely cleaved during the conversion of procollagen type III into collagen type III, remaining to some extent in the final fiber and thus also being released during fiber degradation. Consequently, the stoichiometric ratio between the number of collagen type III molecules produced and the number of PIIICP and PIIINP molecules released may vary.

Biomarkers Related to Collagen Degradation

The degradation of collagen fibers is mediated by the MMP family of enzymes that can be inhibited by direct interaction with naturally occurring, specific tissue inhibitors of metalloproteinases (TIMP-1 to TIMP-4). Interstitial collagenase (MMP-1), neutrophil collagenase (MMP-8), and collagenase-3 (MMP-13) initiate the digestion of collagens by hydrolyzing the peptide bond following a glycine residue located at a distance of three quarters of the collagen molecule length from the amino-terminal extreme. The resulting one-quarter carboxy-terminal telopeptide released by the action of MMP-1 on collagen type I (CITP) is found in an immunochemically intact form in blood (Figure 2). A stoichiometric ratio of 1:1 exists between the number of collagen type I molecules degraded and of CITP molecules released, and the amount of CITP that reaches the circulation.
is proportional to the amount of fibrillar collagen degraded. Therefore, CITP may qualify as an index of MMP-1–dependent collagen type I degradation.

The resulting three-quarter fragment amino-terminal telopeptide released by MMP-1 from the collagen molecule is further degraded by MMP-2 and MMP-9 or gelatinases. The final fragmented matrix peptides or matrikines released by the action of these enzymes have biological activities in the regulation of collagen metabolism and angiogenesis. For instance, the tripeptide glycyl-histidyl-lysine (GHL) derived from collagen type I stimulates new collagen synthesis by fibroblasts. It has also been shown that GHL stimulates MMP-2 expression and secretion by fibroblasts in culture, suggesting a redundant and cooperative role among some MMPs and matrikines. Although the tripeptide GHL can be found in human plasma (Figure 2), its stoichiometry relative to the degradation of the larger collagen type I telopeptide is unknown.

Circulating Biomarkers of Collagen Metabolism in Cardiac Diseases

Alterations of the Myocardial Collagen Network in Cardiac Diseases

Disturbances of collagen metabolism can lead to abnormalities in the architecture and composition (ie, remodeling) of the collagen network that, in turn, will result in alterations of LV morphology and function (reviewed elsewhere). In some cases, increased collagen synthesis over degradation occurs that leads to accumulation of collagen fibers. This includes distinctive patterns of reparative and reactive myocardial fibrosis, each of which alters diastolic myocardial stiffness and facilitates ventricular hypertrophy and diastolic dysfunction (Figure 3). Alternatively, the predominance of degradation over synthesis leads to the disruption and loss of myocardial collagen scaffold and/or decline in matrix tensile strength that can be responsible for ventricular dilatation and systolic dysfunction (Figure 3). Depending on the temporal sequence of the disease process and on the localization, either diffuse or focal, of the injury, these 2 patterns may coexist at variable degrees within the same myocardium (Figure 3). It has been proposed that the aforementioned alterations of the collagen network are present in 4 major types of cardiac diseases: ischemic heart disease, heart disease associated with pressure overload, heart disease associated with volume overload, and intrinsic myocardial disease or cardiomyopathy (Table 1).

Circulating Biomarkers of Collagen Metabolism and Alterations of the Myocardial Collagen Network

Because biomarkers of collagen metabolism present in blood are not cardiac specific, the problem of how to demonstrate their relationship with the lesions of the collagen network present in cardiac diseases emerges. To address this issue, we have proposed that a given circulating biomarker must be investigated to answer a number of questions (Table 2). Because this is an invasive and expensive investigation, not practical for routine assays, published information on this topic is scarce. Nevertheless, some preliminary data are already available that deserve to be considered.

Serum PICP

It has been observed that, in the setting of steady-state production by extracardiac sources, PICP detected in peripheral blood from patients with hypertensive heart disease
(HHD) is mainly of cardiac origin because a positive gradient exists for its serum concentration from the coronary sinus towards antecubital vein in these patients but not in normotensive subjects (Figure 4). PICP has been shown to be associated with myocardial fibrosis in patients with HHD, and patients with idiopathic dilated cardiomyopathy. In addition, PICP is associated with LV mass index and LV chamber stiffness in patients with HHD.20,21,22,23,24,25 Similar associations have been reported in patients with idiopathic dilated cardiomyopathy.25 Besides, it has been shown that PICP concentration, the extent of myocardial fibrosis, and LV chamber stiffness change in parallel in response to antihypertensive therapy in patients with HHD.22,23,24,25 Finally, increased concentrations of PICP detect severe fibrosis and predict HF with preserved ejection fraction in patients with HHD with an acceptable sensitivity and specificity.

Serum PIIINP

Although the cardiac origin of circulating PIIINP in patients with cardiac diseases remains to be proven, an association has been found between PIIINP concentrations and myocardial collagen type III content in patients with ischemic heart disease and patients with idiopathic dilated cardiomyopathy. In addition, an inverse association has been found between PIIINP and transmitral flow parameters assessing diastolic function and longitudinal systolic strain assessing systolic function in patients with HHD. Furthermore, increased PIIINP shows good sensitivity and specificity for predicting HF with preserved ejection fraction in these patients.

Serum CITP

Whereas the pathophysiologically meaning of isolated CITP measurement still remains to be established, this peptide can be used in combination with PICP to assess collagen type I turnover indirectly. In fact, on the basis of data obtained in hypertensive animals, it has been proposed that the circulating PICP:CITP ratio may be an index of the degree of coupling between the synthesis and the degradation of collagen type I. Of interest, the ratio is associated with the severity of myocardial fibrosis in patients with HHD, suggesting that an increased ratio, reflecting the predominance of synthesis over degradation, may lead to fibrosis in these patients.

Plasma MMP-1

A higher concentration of MMP-1 has been found in coronary sinus blood compared with antecubital vein blood in patients with HHD but not in normotensive subjects (Figure 4). Moreover, a highly significant direct correlation has been found between MMP-1 detected in coronary blood and peripheral blood in these patients. Of interest, in patients with HHD and HF, MMP-1 concentration measured in peripheral blood increases in parallel with the increase in

<table>
<thead>
<tr>
<th>Cardiac Diseases</th>
<th>Myocardial Fibrosis</th>
<th>Loss of Myocardial Collagen Scaffold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With previous MI</td>
<td>Develops late within the infarct zone and may appear remote to the infarct zone</td>
<td>Appears early within the infarct zone</td>
</tr>
<tr>
<td>Without previous MI</td>
<td></td>
<td>Parallels the development of HF</td>
</tr>
<tr>
<td>Pressure overload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHD</td>
<td>Accompanies the development of cLVH and diastolic dysfunction</td>
<td>Is associated with the deterioration of systolic function</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Accompanies the development of cLVH</td>
<td></td>
</tr>
<tr>
<td>Volume overload</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Accompanies the development of eLVH</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic cardiomyopathy</td>
<td>Accompanies the development of LVH and LV dysfunction</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Accompanies the development of LVH and LV dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; HHD, hypertensive heart disease; cLVH, concentric LV hypertrophy; and eLVH, eccentric LV hypertrophy.

Table 2. Questions to Be Answered Before a Circulating Molecule Can Be Considered as a Biomarker of the Myocardial Collagen Network

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there an association between its expression or mechanism of production in the myocardium and its blood concentration?</td>
<td>Yes</td>
</tr>
<tr>
<td>Is there a positive gradient from its concentration in coronary sinus blood toward its concentration in peripheral vein blood, thus proving its main cardiac origin?</td>
<td>Yes</td>
</tr>
<tr>
<td>Are there associations of its concentration in blood with the myocardial histopathological alteration and the disturbances of LV morphology and function under study?</td>
<td>Yes</td>
</tr>
<tr>
<td>Do its levels vary in parallel with the changes in the above myocardial alteration and LV disturbances induced by treatment?</td>
<td>Yes</td>
</tr>
<tr>
<td>Does it exhibit adequate diagnostic performance (eg, sensitivity and specificity) to detect the histopathological alterations under study?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
myocardial MMP-1 expression and is higher in patients with loss of myocardial collagen scaffold than in patients without this lesion (Figure 6). In addition, MMP-1 is directly associated with LV end-diastolic volume dimensions (Figure 6) and inversely with ejection fraction (Figure 6) in patients with HHD and HF. Thus, in the setting of steady-state production by extracardiac sources, an excess of circulating MMP-1 in patients with HHD can be considered of cardiac origin. Whereas myocardial MMP-1 expression has been reported to be altered in patients with cardiac diseases associated with either fibrosis (eg, aortic stenosis) or loss of collagen scaffold (eg, idiopathic dilated cardiomyopathy and ischemic heart disease), no studies have been performed to analyze the association of myocardial and circulating MMP-1 in these patients.

**Plasma TIMP-1**

A positive gradient and a direct correlation have been reported between TIMP-1 concentration in coronary sinus blood and TIMP-1 concentration in antecubital vein blood in patients with HHD after exclusion of other extracardiac sources, suggesting the potential cardiac origin of circulating TIMP-1 in these patients. However, the association of the circulating levels of this molecule with its myocardial expression has not yet been demonstrated. Increased TIMP-1 has been found to exhibit good sensitivity and specificity for predicting diastolic dysfunction and HF with preserved ejection fraction in patients with HHD. Interestingly, it has been reported that TIMP-1 is an independent predictor of all-cause mortality risk in patients with chronic HF and that its prognostic information is incremental when added to a set of clinical and biochemical chronic HF descriptors.

On the other hand, it has been proposed that the circulating MMP-1:TIMP-1 ratio may serve as an indirect index of circulating unbound MMP-1. In this regard, an abnormally low MMP-1:TIMP-1 ratio has been found in patients with hypertrophic cardiomyopathy and passive diastolic dysfunction. It has been reported that the circulating MMP-1:TIMP-1 ratio is directly associated with LV end-diastolic diameter and inversely associated with ejection fraction in patients with HHD. Of interest, an association has been reported between the MMP-1:TIMP-1 ratio and the degradation of collagen fibers in patients with idiopathic dilated cardiomyopathy before and after LV assist device support.

**Other Circulating Biomarkers**

Whereas parallel changes in myocardial collagen content and serum PINP have been reported in HF patients presenting reverse LV geometric remodeling after prolonged LV assist device support, no significant correlations were found between the 2 parameters. On the other hand, although plasma MMP-9 levels have been found to be associated with...
late gadolinium enhancement by cardiac magnetic resonance (a potential index of myocardial collagen content) in patients with hypertrophic cardiomyopathy, no data are available in the literature on the association of circulating gelatinases with alterations of the myocardial collagen network in cardiac patients. Finally, there is no available information on serum PIIICP in cardiac diseases.

**Aspects Influencing the Clinical Evaluation of Circulating Biomarkers of Collagen Metabolism**

**Aspects Related to the Immunoassay Method of Detection**

All the aforementioned peptides and proteins can be measured in serum or plasma samples easily, reproducibly, and inexpensively with commercially available ELISAs or radioimmunoassays. However, different commercial kits for the same biomarker may give variable quantitative results, depending on the antibodies and standards used; therefore, it is important to standardize these determinations before applying them to routine clinical practice. More important, this aspect must be taken into account in comparisons of values of 1 biomarker provided by different studies using different methods.

On the other hand, whereas most of the peptides generated during the processing of procollagen types I and III are found as 1 antigen form in serum, PINP appears in 2 different forms: 1 form corresponding to the whole propeptide and a smaller form that is the product of its degradation. It is thus important to use assays that can identify the intact molecule as the biomarker of interest.

**Aspects Related to the Elimination of Circulating Biomarkers From the Circulation**

Another potential confounding factor in the interpretation of blood concentrations of collagen markers is their pathway of elimination. The propeptides PICP and PIIINP are cleared via uptake by endothelial cells in the liver. As a consequence, in conditions of chronic liver insufficiency, the increases in their serum concentrations may reflect reduced hepatic clearance but not increased production. On the other hand, CITP is believed to be cleared through the kidneys because of its small size (≈12 kDa). Thus, a glomerular filtration rate <50 mL·min⁻¹·1.73 m⁻¹ facilitates the increase in CITP serum concentration.

The mechanisms for the clearance of MMPs and TIMPs are not yet fully understood. One mechanism for MMPs may be their own autoproteolysis, as shown for MMP-1. Extracellular MMP concentrations can also be regulated by direct clearance of the intact proteins via low-density lipoprotein–related scavenger receptors and subsequent degradation. In addition, cleavage of α₂-macroglobulin by most MMPs induces a conformational change that irreversibly traps the enzyme. This complex is eventually endocytosed and degraded. Of interest, MMP-1 bound to α₂-macroglobulin is not recognized by most of the kits for the detection of circulating MMP-1.

**Aspects Related to the Demographics of the Subjects**

It is important to note that the serum concentrations of some of the above biomarkers may change as a function of demographics in the absence of cardiovascular disease. For instance, in infants and children, serum PICP concentration correlates with growth velocity; thus, it is physiologically increased in these populations. On the other hand, in community-based studies, it has been reported that PIIINP levels increased with age and body mass index and that TIMP-1 levels increased with age and male sex. Thus, the confounding influence of these factors must be excluded in all studies of circulating biomarkers of collagen metabolism.

**Aspects Related to the Presence of Comorbidities**

Taking into account the diversity of tissue sources of collagen biomarkers considered here, changes in their blood levels...
may be related not to alterations of the myocardial collagen network but to alterations of collagen in other organs. Some preliminary data suggest that changes in concentrations of some of these biomarkers present in patients with vascular diseases represent integrated abnormalities of the cardiovascular collagen. For instance, it has been reported that arterial stiffness was directly correlated with serum PICP in elderly hypertensive patients. Although no cardiac parameters were included in a multiple regression analysis to assess whether they influenced the correlations between arterial stiffness and serum biomarkers, these observations suggest that in arterial hypertension, alterations in these molecules may reflect disturbances of collagen metabolism that occur not just at the myocardial but also at the arterial wall level.

On the other hand, the presence of concomitant noncardiovascular diseases affecting collagen matrix can also affect the circulating levels of these molecules because none of them are exclusively from a cardiac origin (Table 3). This means that before changes in blood concentrations of biomarkers of collagen metabolism can be specifically attributed to alterations of the myocardial collagen scaffold, just a few meet this require-

### Table 3. Alterations of Circulating Collagen-Derived Peptides in Patients With Noncardiac Diseases

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Major Alterations of Serum Biomarkers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic bone disease (cancer of the breast, lung, prostate, and other sites)</td>
<td>&gt;CTP</td>
<td>55</td>
</tr>
<tr>
<td>Metabolic bone disease (severe osteoporosis)</td>
<td>&gt;PICP, &gt;PINP</td>
<td>56</td>
</tr>
<tr>
<td>Chronic liver diseases (cirrhosis of different origins)</td>
<td>&gt;PIIINP</td>
<td>57</td>
</tr>
<tr>
<td>Chronic kidney disease (stages 4 and 5 with high-turnover bone disease)</td>
<td>&gt;PICP, &gt;CTP</td>
<td>58</td>
</tr>
<tr>
<td>Other inflammatory and fibrogenic diseases</td>
<td>Osteoarthritis, rheumatoid arthritis &gt;PIIINP, &gt;CTP</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Diffuse fibrosing lung disease &gt;PICP, &gt;CTP</td>
<td>60</td>
</tr>
</tbody>
</table>

> Indicates abnormally increased level or ratio.

Aspects Related to the Effects of Pharmacological Treatment

Finally, it is of note that long-term pharmacological treatment, namely with drugs used to treat cardiovascular diseases, may modify the serum levels of biomarkers of collagen metabolism. For instance, it has been reported that serum PICP decreases in hypertensive patients being treated with angiotensin type 1 receptor antagonists or HF patients treated with the loop diuretic torasemide. PIINP decreases in HF patients treated with aldosterone antagonists, CITP and MMP-1 increase in hypertensive patients treated with angiotensin-converting enzyme inhibitors, and CITP decreases in hypercholesterolemic patients treated with statins. Thus, the potential influence of previous pharmacological treatment must be carefully considered in studies assessing serum biomarkers of collagen metabolism in cardiac patients.

### Table 4. Alterations of Circulating Biomarkers of Collagen Metabolism in Patients With Cardiac Diseases Associated With Lesions of the Collagen Network

<table>
<thead>
<tr>
<th>Cardiac Diseases</th>
<th>&gt;PICP</th>
<th>&gt;PICP:CTP</th>
<th>&gt;PIIINP</th>
<th>&gt;MMP-1</th>
<th>&gt;MMP-1:TIMP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive heart disease</td>
<td>20, 21, 28–30, 61, 62, 88</td>
<td>22, 28</td>
<td>23, 32, 88–90</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mitral regurgitation</td>
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<td>Idiopathic dilated cardiomyopathy</td>
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<tr>
<td>Diabetic cardiomyopathy</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
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</tbody>
</table>

> Indicates abnormally increased level or ratio. Numbers are references.
ment and thus provide information on potential clinical usefulness (Table 4). Of interest, some of these studies report alterations in >1 biomarker, thus providing the opportunity for a several-biomarker combination as a more informative approach to the alterations of collagen metabolism under study.

Conclusions and Future Directions

Despite the available information on circulating biomarkers of collagen metabolism, a number of major limitations remain that weaken their clinical usefulness. It is likely that these limitations are the result of the lack of adequate strategies to investigate a given biomarker from its pathobiological fundamentals to its assessment in clinical practice. Therefore, the time has come for collaborative research initiatives aimed at definitively covering in an integrated manner the following aspects: (1) demonstration of the connections between the measured levels of the molecules proposed as biomarkers, the lesions of the myocardial collagen network, and the alterations of LV anatomy and function; (2) prospective validation of incremental information provided by a multimarker strategy combining these molecules with standard biochemical markers (eg, circulating natriuretic peptides) and emerging genetic and imaging markers in independent populations; (3) assessment of effects of their measurements on patient management and outcomes; and (4) evaluation of the feasibility and cost-effectiveness of the application of this strategy in the community. With the information provided in this review, some biomarkers emerge as the most appropriate candidates for initiating such a collaborative research.

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Disclosures

None.

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