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Serum Copeptin in Cardiooncology Practice: Review of Pathophysiological and Clinical Implications

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In cardiooncology practice, "early cardiotoxicity" refers to an emerging subclinical myocardial dysfunction/injury in response to certain chemotherapeutic regimens. This condition can progress to overt cardiotoxicity in time and hence warrants proper and timely diagnostic and preventive strategies. Current diagnostic strategies for "early cardiotoxicity" are largely based on conventional biomarkers and certain echocardiographic indices. However, a significant gap still exists in this setting, warranting further strategies to improve diagnosis and overall prognosis in cancer survivors. Copeptin (surrogate marker of the arginine vasopressine axis) might serve as a promising adjunctive guide for the timely detection, risk stratification, and management of early cardiotoxicity on top of conventional strategies largely due to its multifaceted pathophysiological implications in the clinical setting. This work aims to focus on serum copeptin as a marker of "early cardiotoxicity" and its general clinical implications in patients with cancer.

In the recent decades, cardiotoxicity among cancer survivors has risen as a significant clinical challenge associated with unfavorable prognosis.[1-4] In general, the adverse impact of cancer on the cardiovascular system could be attributed to cancer management strategies, including chemotherapy and radiotherapy, and usually presents with a variety of cardiovascular manifestations, including heart failure (HF) and hypertension (HT).[1-5] In the setting of cancer, "cardiotoxicity" encompasses a form of new-onset or worsening cardiomyopathy in response to certain chemotherapeutic regimens, including anthracyclins.[1-3] By definition, cardiotoxicity refers to a 10% point reduction in the left ventricular ejection fraction (LVEF) value from baseline to a final value of <53% (or 50%) in the setting of previously normal systolic functions.[1-6] Cardiotoxicity has been categorized into two distinct types according to its recovery pattern: irreversible or minimally reversible (namely type-1 and usually associated with anthracyclines [such as doxorubicin and epirubicin] and cyclophosphamide in a dose-dependent manner) and reversible (namely type-2 and usually associated with trastuzumab and lapatinib in a nondose dependent manner).[1-3] This condition has a poor prognosis, particularly in the setting of anthracyline chemotherapy.[7] Cardiooncology guidelines suggest a variety of baseline risk factors for cardiotoxicity, including young or old age, female gender, planned high-dose chemotherapy (250 mg/m^2 for doxorubicin), concomitant chemo or radiotherapy, HF (with low or normal LVEF), renal failure, cardiovascular risk factors (arterial HT, smoking, diabetes mellitus), and genetic predisposition.[1]

"Early cardiotoxicity" is defined as a new-onset subclinical myocardial dysfunction/injury in response to a certain cardiotoxic chemotherapy cycle and serves as a stronger predictor of late cardiomyopathy (cardiotoxicity) in this setting.[1,8-10] Certain biomarkers, including high-sensitive troponin (hsTn) and natriuretic peptides (such as N-terminal pro-brain natriuretic peptide [NT-proBNP]), and certain echocardiographic indices, including global longitudinal strain (GLS) (>15% reduction compared with baseline), have been routinely recommended for detecting early cardiotoxicity following each cycle of cardiotoxic chemotherapy (including anthracyclins).[1,9-15] The practical value of less known biomarkers, including galectin-3, meyeloperoxidase,[9] adropin (a

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protein associated with lipid and glucose homeostasis,[16] endothelin (ET), glycogen phosphorylase isoenzyme BB, fatty acid binding protein, and interleukin-6 (IL-6), and certain microRNAs (miRs), including miR-208, miR-216, and miR-29,[10,11,16,17] remain to be fully established in the clinical setting. An integrated approach (combined evaluation of conventional biomarkers and tools) is highly recommended to improve the detection of early cardiotoxicity.[18]

Once early cardiotoxicity is documented, a variety of protective strategies[11-15] should be implemented to prevent further progression to overt cardiac dysfunction. Current protective strategies include agents with specific actions, including dextrazoxane (an iron chelating agent administered concomitantly with doxorubicin infusion in patients with planned high-dose chemotherapy regardless of increased biomarker levels), certain ß blockers (such as carvedilol), renin-angiotensin-aldosterone-system (RAAS) blockers (such as candesartan and perindopril), statins, and certain antioxidants (such as coenzyme-Q) and lifestyle modifications, including aerobic exercise; all of which have demonstrated variable rates of therapeutic benefit in this setting.[11-15] However, under or overtreatment with the above-mentioned agents (largely due to the misdiagnosis of early cardiotoxicity) remains a therapeutic challenge in patients with cancer.

Notwithstanding the routine use of conventional biomarkers and certain echocardiographic indices, a significant gap still exists in the absolute detection of early cardiotoxicity. Conventional strategies, even those introduced in an integrated approach, have significant limitations and appear to be far from perfection. Hence, additional strategies are still warranted in clinical practice. Copeptin (C-terminal provasopressine), a novel biomarker of the AVP axis might serve as an adjunctive rule-in or rule-out efficient marker of early cardiotoxicity among cancer survivors receiving chemotherapy due to its multifaceted implications and superior features. Furthermore, the evaluation of serum copeptin might allow risk stratification and hence proper management of early cardiotoxicity. In this work, we aim to discuss serum copeptin as a marker of early cardiotoxicity and its general pathophysiological and clinical implications in the setting of cancer.

COPEPTIN: UNIQUE BIOMARKER WITH MULTIFACETED CHAREACTERISTICS

General features

In the past years, copeptin has gained widespread recognition as the novel neurohormone of the AVP system due to its important clinical implications and diverse characteristics.[19-21] Structurally, it is a glycosylated polypeptide with 39 amino acids and is synthesized in the hypothalamus through the stepwise enzymatic cleavage of the 164 amino acid precursor peptide, namely, preprovasopressin that primarily comprises neurophysin-2, signal peptide, AVP (also known as antidiuretic hormone [ADH]) and copeptin.[21-22] Following their axonal transport to neurohypophysis, AVP and copeptin are co-released systemically (in an equimolar fashion) in response to osmotic (hypertonicity) and hemodynamic (hypovolemia, hypoperfusion) triggers as the final step.[20-24] Therefore, a strong correlation exists between serum AVP and copeptin levels.[20-24] Copeptin also harbors structural and methodological advantages, favoring its proper quantification.[20]

As opposed to the well-known physiological actions of AVP through a variety of receptors (including V1a (systemic vasoconstriction), V1b (humoral changes), and V2 (renal water reabsorption) receptors), the functions of copeptin are poorly understood and mostly speculated as acting as a carrier of AVP in the course of its axonal transportation and being involved in the proteolytic maturation of the precursor hormone.[20-24] Copeptin was previously suggested to have a median plasma level of 4.2 pmol/l. In contrast to that of natriuretic peptides, its plasma level are not significantly influenced by clinical variables including gender, age, and obesity.[20-24] Copeptin has a relatively low specificity but high sensitivity and hence might be used as a rule-out marker (with a considerably high negative predictive value) in a wide array of clinical presentations, including acute coronary syndromes.[20,21,24]

Pathophysiological and clinical implications

Clinically, copeptin generally serves as the surrogate peptide of the AVP system largely owing to its equimolar secretion kinetics with the sister neurohormone AVP and its stable molecular characteristics that offer methodological advantages (compared with AVP).[20-24] Copeptin quantitatively mirrors AVP and hence the pathophysiological impact of AVP on various organ systems.[20-24] Pathophysiologically, AVP has autonomic implications characterized by its strong correlation with the adrenergic system (and hence endogenous stress levels) partly due to the impact of noradrenaline and angiotensin-2 on its release from the hypothalamus (neurohypophysis).[20,21,25] Moreover, AVP may have a fibrogenic impact on various cardiac structures (myocardium and valvular tissues) as substantiated by experimental studies demonstrating its significant effects on myocardial protein and collagen synthesis, ultimately leading to myocardial hypertrophy.[20,26,27] Finally, AVP has hemodynamic implications and is strongly correlated with the severity of systemic hypoperfusion.[19,28]

Largely based on the above-mentioned autonomic, fibrogenic, and hemodynamic implications of the AVP system, copeptin (regarded as the surrogate of this system) has been demonstrated to work as a diagnostic, prognostic, and therapeutic marker in various cardiovascular and noncardiovascular diseases.[20] In addition to its diagnostic value in primary disorders of AVP, including diabetes insipidus[29,30] and syndrome of inappropriate ADH secretion (SIADH),[31] copeptin also functions as a prognostic marker in certain noncardiovascular pathologies, including septic shock,[32] pneumonia,[33] and traumatic brain injury[34] due to its strong correlation with endogenous stress levels or hemodynamic compromise associated with the severity of the underlying condition. It also serves as a crucial marker for cardiovascular disease. Owing to its high sensitivity, copeptin excludes acute myocardial infarction (AMI) in a rapid and safe manner, particularly in combination with troponin evaluation.[20,35] It also has a strong prognostic value in various cardiovascular conditions, including congestive HF, stroke, and takotsubo cardiomyopathy.[20,36-38]

Copeptin elevation in cancer

In the clinical setting, serum copeptin might reach substantially elevated levels in some patients with cancer due to a variety of factors (mostly in combination).

Enhanced stress response: General stress response in patients with cancer might significantly contribute to the elevation of their copeptin levels. The AVP axis and copeptin serve as a nonspecific stress marker exhibiting a strong correlation with endogenous stress levels.[20] In addition to being associated with adrenergic hyperactivation, the AVP axis works in concert with corticotrophin-releasing hormones to stimulate adrenocorticotrophic hormone release from hypophysis with subsequent enhancement of cortisol synthesis in the adrenal glands.[20,39] Therefore, a strong interaction exists among adrenergic, AVP, and corticotrophic systems for the orchestration of stress response as in the setting of severe illnesses[20,39] including cancer. Despite being regarded as a systemically inert neurohormone, copeptin is placed at the center of this endogenous stress response cascade with important prognostic implications in the setting of severe diseases[20] such as cancer. Accordingly, copeptin was previously reported to be significantly higher in medical and surgical patients compared with that in controls,[40] suggesting endogenous stress as a crucial determinant of copeptin levels.

In the setting of active malignancy, patients might have significant levels of inflammatory burden and might suffer intractable pain, cachexia, and adverse effects of management strategies,[41] all of which might serve as substantial physical stressors. In addition, anxiety associated with fear of clinical deterioration and social restriction might significantly contribute to emotional stress in patients with cancer.[42] Therefore, copeptin levels might significantly increase as part of the general stress response[20] in patients with cancer, usually in correlation with the magnitude of the underlying stressors. In this context, copeptin may also serve as a therapeutic guide while combating the underlying stressor in this specific population.

Ectopic AVP production: As paraneoplastic syndromes, SIADH and associated hyponatremia may be encountered in aggressive cancer types, such as small-cell lung cancer (up to 70% of cases) and head–neck tumors, and certain types of solid and hematological malignancies[43] and might be associated with substantial levels of copeptin.[31] Certain treatment modalities in patients with cancer may also significantly contribute to the evolution of this phenomenon.[43,44] Given that AVP secretion in patients with SIADH appears to be autonomous and persistent despite low serum osmolality,[43,44] serum copeptin levels may be extremely higher in this setting compared with other triggers of copeptin elevation. Therefore, extremely high copeptin levels in association with certain biochemical parameters including hyponatremia, low serum osmolality (values of < 275 mOsm/kg), and increased urine osmolality in the absence of other triggers (such as adrenal dysfunction and diuretic use) might be suggestive of SIADH in the setting of cancer.[31,43,44] In addition to its prognostic implications (potentially mirroring tumor burden leading to SIADH), serum copeptin might help monitor the course of cancer (such as tumor activity and recurrence) following specific management strategies and might serve as a therapeutic guide in the setting of malignancies associated with SIADH.

Miscellaneous complications, including superimposed infections, septic (or hemorrhagic) shock, stroke, HF, and TTC, might also contribute to serum copeptin elevation[20,38,45-47] in the setting of cancer. However, the clinical implications of copeptin associated with these conditions[20] in patients with and without cancer are generally similar. As described later, copeptin might also serve as a promising marker of early cardiotoxicity and aid in the diagnosis and management of this ominous phenomenon.

CURRENT STRATEGIES HAVE SIGNIFICANT LIMITATIONS IN THE DIAGNOSIS OF EARLY CARDIOTOXICITY

Conventional markers have been highly recommended for the diagnosis of early cardiotoxicity. In a previous study, patients with persistent elevation of troponin-I (TnI) (positive immediately after chemotherapy and after 1 month) following high-dose chemotherapy showed a significant reduction in LVEF values and high frequency of cardiac events on follow-up compared with those with transiently elevated (positive only after chemotherapy cycle and returning normal limits thereafter) or troponin-I levels within normal limits.[12] In another study on patients receiving standard dose of mitoxanthrone or anthracyclin, troponin-T (TnT) positivity was found to be associated with a significant reduction in LVEF values at year 1.[13] Similarly, the potential value of natriuretic peptides (with variable sensitivity and specificity values) in this setting has been investigated.[11,14,15] The persistent elevation of NT-proBNP at 72 h following a cardiotoxic chemotherapy cycle was reported to be associated with a significant decline in LVEF values on follow-up.[14]

Despite being highly recommended in clinical practice, troponins and natriuretic peptides are nonspecific for the absolute detection of early cardiotoxicity, leading to overdiagnosis in some patients with cancer. Studies suggested the unreliable nature of conventional markers in this setting. In a previous research on patients with breast cancer treated with trastuzumab,[48] only 62% of patients with TnI elevation (as compared with 5% of patients without TnI) suffered late cardiomyopathy, even though TnI elevation was suggested as the only independent predictor of overt cardiotoxicity. This finding suggested the moderate positive predictive value of this biomarker (largely due to its lower specificity[49]) when used in isolation in this setting. The same phenomenon might hold true for natriuretic peptides including NT-proBNP, BNP, and N-terminal proatrial natriuretic peptide that have failed to predict cardiotoxicity.[18,50,51]

Furthermore, the sensitivity of these markers may not be high, implying that some patients with cancer might still suffer from unexpected late cardiomyopathy even in the absence of antecedent alterations in biomarker levels[18] and echocardiographic findings. Previous studies on patients with cancer with late cardiotoxicity following anthracyclins or trastuzumab treatment found no significant increase in the levels of conventional biomarkers including TnT and BNP, as opposed to early significant changes in certain echocardiographic indices including Tei index, radial,

and longitudinal strain.[18,52,53] This finding indicated the need for specific and sensitive markers in this setting.

An integrated approach is generally recommended to combat diagnostic challenges associated with conventional markers.[18] However, misdiagnosis is possible even with an integrated approach. On the one hand, normal GLS value in combination with a normal troponin level exhibited a negative predictive value of 91% for the future evolution of overt cardiotoxicity.[9] On the other hand, a 10% decrease in GLS along with TnI elevation relative to baseline in response to anthracycline and trastuzumab therapy showed a positive predictive value of around 80% for detecting cardiotoxicity.[18]

The under or overdiagnosis of early cardiotoxicity might lead to the mismanagement of patients with cancer. Overtreatment with preventive strategies in an unnecessary and aggressive manner might be associated with certain adverse outcomes (largely due to the side effects of these strategies, including hypotension and renal or hepatic failure) in these already fragile subjects. Undertreatment in this setting might speed up the evolution of overt cardiomyopathy, which is known for its unfavorable prognosis. Therefore, the incorporation of further biomarkers including copeptin (with superior features including extremely high sensitivity) into the integrated approach may lead to diagnostic and therapeutic improvement in this setting.

SERUM COPEPTIN MIGHT AID IN THE DETECTION OF EARLY CARDIOTOXICITY DUE TO THE PATHOPHYSIOLOGICAL IMPLICATIONS OF THE AVP AXIS IN EARLY CARDIOTOXICITY

Besides the aforementioned implications in patients with cancer, copeptin might serve as an adjunctive marker of early cardiotoxicity, and hence; might be incorporated, on top of conventional strategies, into clinical practice largely due to its pathophysiological implications in this setting. In the clinical setting, the association between early cardiotoxicity and activation of the AVP axis (as demonstrated with copeptin elevation) appears to be bidirectional, implying that one may have the potential to trigger the other through a variety of direct or indirect mechanisms:

Subclinical myocardial dysfunction/injury associated with early cardiotoxicity might lead to a significant and persistent elevation of serum copeptin

Systemic hypoperfusion is a characteristic feature of certain serious conditions, including advanced HF, and serves as a strong trigger of AVP axis and copeptin release even in the presence of plasma hypotonicity, a condition frequently encountered in patients with HF.[20] Serum copeptin and AVP levels were previously demonstrated to exhibit an inverse correlation with cardiac index and LVEF values.[19,28] Regardless of the underlying etiology, chronic HF syndromes commence as a subclinical phenomenon that generally progresses to clinical HF in time.[54] Subclinical myocardial dysfunction is characterized by normal systolic and diastolic functions at rest as demonstrated with conventional echocardiograms usually accompanied by subtle abnormalities in tissue Doppler parameters and myocardial deformation indices (strain, strain rate)[55-57] and persistent elevation of certain biomarkers, including myocardial enzymes, natriuretic peptides, and a variety of specific fibrogenic and inflammatory markers.[54] Patients with subclinical myocardial dysfunction generally suffer fatigue, dyspnea, and reduced exercise capacity[54-56] largely attributable to bouts of overt HF (leading to pulmonary congestion and disproportionately (or absolutely) low levels of systemic perfusion) at the time of exercise.

Within this context, early cardiotoxicity, based on the above-mentioned notions, might be considered as an epitome of subclinical myocardial dysfunction, and hence; might present with bouts of exercise-induced HF leading to the stimulation of AVP axis (and elevation of serum copeptin) along with other systems (RAAS, adrenergic system, and natriuretic peptides) as part of neurohormonal activation.[20] Accordingly, in an experimental study, the elevation of plasma copeptin was demonstrated in rats treated with doxorubicin, possibly as a consequence of emerging HF and significant hemodynamic changes in this setting.[17] Interestingly, endocardial and myocardial copeptin expressions were shown to be significantly reduced (as opposed to plasma levels) in these rats, suggesting the role of doxorubicin-induced inhibition of local copeptin production potentially associated with the evolution of cardiotoxicity in this setting.[17] However, it might also be suggested that the elevation of plasma copeptin in these rats,[17] besides being as a consequence of central (hypothalamic) copeptin release due to hemodynamic deterioration, might also be attributable to the cardiac copeptin spill-over into the circulation associated with myocardial and endocardial injury, possibly as a result of doxorubicin toxicity (as analogous to the setting of troponin elevation). Moreover, a previous experimental study on rats[58] demonstrated cardiac AVP production and its systemic release in response to enhanced myocardial wall stress (potentially analogous to the setting of natriuretic peptide synthesis and release), suggesting the cardiovascular system as an additional source of copeptin (though not substantiated in a recent clinical study on AMI patients[59]). Therefore, even though neurohormonal activation seems to be the dominant mechanism of copeptin elevation in the setting of early cardiotoxicity, myocardial changes (injury, enhanced wall stress during exercise) might also significantly contribute to its elevation in this setting. In this context, the multifaceted release kinetics of copeptin might further enhance its diagnostic sensitivity and specificity (as compared with other biomarkers) in the detection of early cardiotoxicity even when used as a single marker strategy.

The long half-lives of inert peptides including NT pro-BNP (120 min) and copeptin (86 min) [as compared with their physiologically-active sister neurohormones including BNP (20 min) and AVP (5-20 min)][59-61] might allow for the proper detection or exclusion of early cardiotoxicity that likely trigger intermittent (rather than sustained) neurohormonal activation, particularly during bouts of stress, including exercise. Accordingly, copeptin elevation as compared with baseline, owing to its structural and methodological advantages,[20] might still appear to be significant even several hours after exertion in ambulatory patients with cancer. Copeptin elevation as part of neurohormonal activation

might be less pronounced or insignificant in sedentary or bedridden patients with cancer.

In summary, serum copeptin might significantly elevate after a cardiotoxic chemotherapy cycle due to an emerging subclinical myocardial dysfunction/injury with consequent neurohormonal activation. Neurohormonal activation in this setting can be regarded not only as a consequence but as a substantial in the perpetuation and even progression to late cardiotoxicity. The positive loop among certain neurohormones (such as AVP axis, adrenergic system, and RAAS) is a well-known clinical and experimental phenomenon[20] that might further accelerate the transition to overt cardiotoxicity in this setting. These notions also provide a strong rationale behind the use of RAAS and ß blockers[1,11,15] (in combination where appropriate) as conventional preventive strategies in clinical practice.

Enhanced AVP actions (as measured with copeptin levels) due to certain chemotherapeutic regimens may significantly contribute to cardiotoxicity

As mentioned previously, the enhanced actions of AVP system have a strong impact on myocardial protein and collagen synthesis and are potentially associated with myocardial hypertrophy and remodeling in the long term.[20-26,27,62] Although, V1 receptor is the primary AVP receptor within the myocardium, V2 receptor and other less well -known vasopressin receptor subtypes including central (V3) and oxytocin (OT) receptors might also mediate the myocardial effects of vasopressin[63]. In addition to accounting for progressive myocardial changes,[20-26,27] enhanced AVP actions were previously demonstrated to exert relatively acute effects on myocardium largely through coronary vasoconstriction (potentially leading to myocardial injury), baroreflex -mediated cardiac inhibition, increased phosphorylase activity (with reduced intracellular glycogen), and through changes in AVP receptor subtypes in certain settings (as exemplified by a substantial reduction in OT receptors leading to acute contractile dysfunction in the setting of ischemia-reperfusion injury).[63-66] The increased AVP levels associated with these adverse effects may be attributed to a variety of endogenous (SIADH) or exogenous (vasopressin infusion) sources in the clinical setting.[65]

In this context, certain chemotherapeutic agents including vincristine, vinblastine, alkylating agents (cyclophosphamide, ifosfamide, melphalan), platinum compounds (carboplatin, cisplatin), methotrexate, pentostatin, and monoclonal antibodies (such as trastuzumab and bevacizumab) were previously suggested to trigger AVP secretion (generally presenting with signs of SIADH including hyponatremia) largely due to their adverse neurotoxic effects on hypothalamus-pituitary axis.[43,67-69] Among these, alkylating agents, platinum compounds, and monoclonal antibodies are also universally renowned for their direct cardiotoxic potential through a variety of mechanisms including mitochondrial dysfunction, reactive oxygen species formation, vascular injury (alkylating agents), blunted angiogenesis (bevacizumab), and mitigation of human epidermal growth factor receptor-2 (HER2) (anti-HER2)/ErbB2 signaling associated with mitochondrial disruption and ATP depletion (trastuzumab).[1-4,9] However, enhanced AVP release with consequent adverse myocardial effects may also play a contributory role in the evolution of cardiotoxicity associated with these agents.

In particular, trastuzumab has been widely used in breast patients with cancer, and is well-known to be associated with a reversible form of cardiotoxicity (type-2) due to contractile dysfunction, etc. in a nondose -dependent manner.[1-4,9] Interestingly, cardiomyopathy associated with this agent might be irreversible or partly reversible in certain susceptible patients[9] suggesting a potential role of progressive adverse remodeling, coronary vasoconstriction etc. induced by enhanced AVP actions due to trastuzumab therapy (on top of its direct and transient impact on myocardium) in these patients. This potentially implies that enhanced AVP release associated with chemotherapeutic agents might not only be associated with the type of agent but might also exhibit an individual heterogeneity. The potential contribution of AVP system in this setting might also help comprehend, in rare instances, the unexpected occurrence of cardiotoxicity due to certain agents that are universally well-known to be devoid of toxic myocardial effects; yet with a potential impact on AVP secretion. However, these notions remain speculative, and should be tested through further studies.

On the other hand, the direct impact of anthracyclines on AVP release and its consequences have yet remained to be fully established. However, as described in the next paragraph, these agents may also be associated with central AVP release through indirect mechanisms. Over recent years, anthracyclines, besides their well -known impact on lipid peroxidation, oxidation of contractile proteins, inhibition of topoisomerase 2B, etc. in a dose-dependent manner)[1-4,9] have also been suggested to exert a variety of pleiotropic harmful effects on myocardium largely governed through induction of certain mediators.[70] One such mediator, ET-1 (a well-known 21 amino acid vasoactive peptide primarily released from vascular endothelial and smooth muscle cells along with cardiomyocytes and usually acting in a paracrine or autocrine fashion[71]) was experimentally reported to be upregulated via doxorubicin-mediated activation of epidermal growth factor receptor with consequent MEK 1/2- ERK 1/2 signaling, and might have important pathogenic implications in doxorubicin-associated cardiomyopathy through enhanced angiogenesis, cellular growth, lipid peroxidation, and induction of tumor necrosis alpha (TNF-alpha) (probably through the stimulation of pro-apoptotic cardiac peptides including Bax).[70] Bosentan, an ET receptor antagonist, was also shown to abolish these detrimental consequences in an experimental model, corroborating the substantial role of ET-1 in doxorubicin-associated cardiomyopathy.[70] Clinically, ET-1 was previously reported to rise progressively during doxorubicin therapy in patients with breast and small-cell lung cancer who later developed HF, suggesting ET-1 as a marker of doxorubicin-associated cardiotoxicity.[72]

ET, along with its receptors, abundantly exists within the central nervous system and serves as a crucial neurotransmitter that modulates central adrenergic discharge and the release of

neurohypophyseal hormones, including AVP.[73-75] The adverse impact of ET-1 in the setting of doxorubicin-associated cardiotoxicity might be mediated through enhanced AVP actions (in correlation with copeptin levels). AVP (along with angiotensin-2) was also previously shown to induce ET-1 release from endothelial cells via intracellular calcium mobilization and protein kinase-C stimulation in these cells.[76] Therefore; enhanced AVP actions already triggered by the central impact of ET-1[73-75] in early cardiotoxicity might further trigger ET-1 release at the periphery,[76] creating a strong positive loop between these two mediators that might primarily account for the perpetuation and rapid progression of doxorubicin-associated cardiomyopathy. This finding also implied that ET-1 might contribute to the cardiotoxic potential of certain chemotherapeutics other than doxorubicin including cyclophosphamide and cisplatin with well-known effects on AVP release. In documenting the magnitude of involvement of AVP and ET systems in early cardiotoxicity, a practical and reliable approach is to measure serum copeptin (or possibly C-terminal pro-ET (CT-pro-ET)) as a surrogate marker of both systems (instead of serum ET-1 with a shorter half-life [1-2 min] that exhibits unstable structural and physiological characteristics potentially hampering its reliable quantification[71] as compared with these markers). In summary, the potential causative role of AVP axis with enhanced ET-1 actions in the setting of early cardiotoxicity suggested that AVP antagonism (tolvaptan) in combination with well-known preventive strategies might be of therapeutic benefit for the prevention of late cardiotoxicity associated with anthracyclins and other cardiotoxic agents.

The lack of significant cardiomyotoxic effects of certain nonchemotherapeutics associated with enhanced AVP actions (including antidepressants, antipsychotics, antiepileptics, opiates, and antidiabetics including chlorpropamide and tolbutamide[69]) in the clinical setting can be explained as follows. First, this phenomenon can be attributed to the relatively short-term and weak impact of these agents on the AVP axis as opposed to chemotherapeutics, which have a widespread and persistent tissue distribution that lead to a sustained central AVP release and is possibly associated with significant central neurotoxicity. Accordingly, many anticancer drugs, regardless of whether they cross the blood brain barrier or not, can induce chronic central neurotoxicity through a variety of poorly understood mechanisms.[77] Second, as previously demonstrated in the setting of myocardial ischemia-reperfusion injury,[63] concomitant cardiomyocyte injury directly induced by these chemotherapeutics (that is not encountered with the use of nonchemotherapeutics associated with enhanced AVP actions) might induce the detrimental effects of enhanced AVP actions through significant alterations in cardiac AVP receptor subtypes. However, these notions should be further tested in experimental and clinical studies.

In summary, enhanced AVP release (as measured with serum copeptin levels) potentially serves either as a consequence of or contributor to (or most likely both) early cardiotoxicity with potential diagnostic and therapeutic implications. Figure 1 shows the pathophysiological implications of serum copeptin (along with associated neurohormones) in the setting of chemotherapy-related early cardiotoxicity. According to studies of HF management with AVP antagonism,[20,21,39] substantial copeptin elevation relative to baseline following a cardiotoxic chemotherapy cycle might allow the identification of patients most likely to benefit from AVP and ET-1 antagonism and conventional modalities, including RAAS and ß blockers. However, AVP antagonism still appears to be at a speculative level in this setting. By contrast, endothelin-1 receptor blockers have been exclusively demonstrated to be of therapeutic value in a couple of experimental studies. Finally, clinical and experimental studies are strongly needed to confirm the practical implications of copeptin in isolated radiation-induced cardiotoxicity.

PRACTICAL USE OF COPEPTIN FOR DIAGNOSIS, RISK STRATIFICATION, AND MANAGEMENT OF EARLY CARDIOTOXICITY

Cardiotoxicity due to various agents remains a potential challenge in clinical practice. In addition to clinical trials, experimental studies tested a variety of diagnostic and therapeutic strategies to combat cardiotoxicity in a timely and proper manner.[78,79] As previously mentioned, a variety of diagnostic strategies and certain biomarkers are available for the diagnosis of early cardiotoxicity with variable sensitivity and specificity values (mostly used in an integrated approach) in the setting of cancer.[9,18] Copeptin as a marker of early cardiotoxicity has also been mentioned in literature.[10,17,80,81] However, these reports generally lack specific recommendations on how and when to harness this specific neurohormone in this setting. In a recent study comprising 108 patients (26 with anal and 82 with colorectal cancer), the serum copeptin levels (but not troponin I levels) were reported to increase significantly after the first 5-FU cycle and progressively increase (despite the constant serum troponin I levels) during subsequent 5-FU cycles.[80] These findings substantiated the diagnostic value of serum copeptin as a marker of 5-FU-related cardiotoxicity.[80] Another experimental study found increased serum levels of copeptin, adropin, and irisin but paradoxically decreased myocardial levels of copeptin in doxorubicin-treated male rats.[17] These findings suggested that myocardium is an important source of serum copeptin that might significantly elevate in case of doxorubicin-related cardiotoxicity.[17] In a large-scale study comprising 555 patients with cancer, the serum levels of copeptin and cardiac markers were found to be associated with all-cause mortality and were already elevated prior to chemotherapy.[81] These findings implied that the measurement of cardiac biomarkers (including copeptin) at baseline and following chemotherapy seems to be imperative for the absolute diagnosis and risk stratification of cardiotoxicity. Given that copeptin might harbor a variety of direct and indirect implications in the setting of cardiotoxicity, the integration of this novel biomarker into routine strategies might significantly enhance the diagnostic sensitivity and specificity of these strategies in the detection of early cardiotoxicity and allow for the improved risk stratification and implementation of proper and timely preventive strategies in this setting.

The concomitant elevation of serum copeptin following chemotherapy in patients with a high likelihood of early

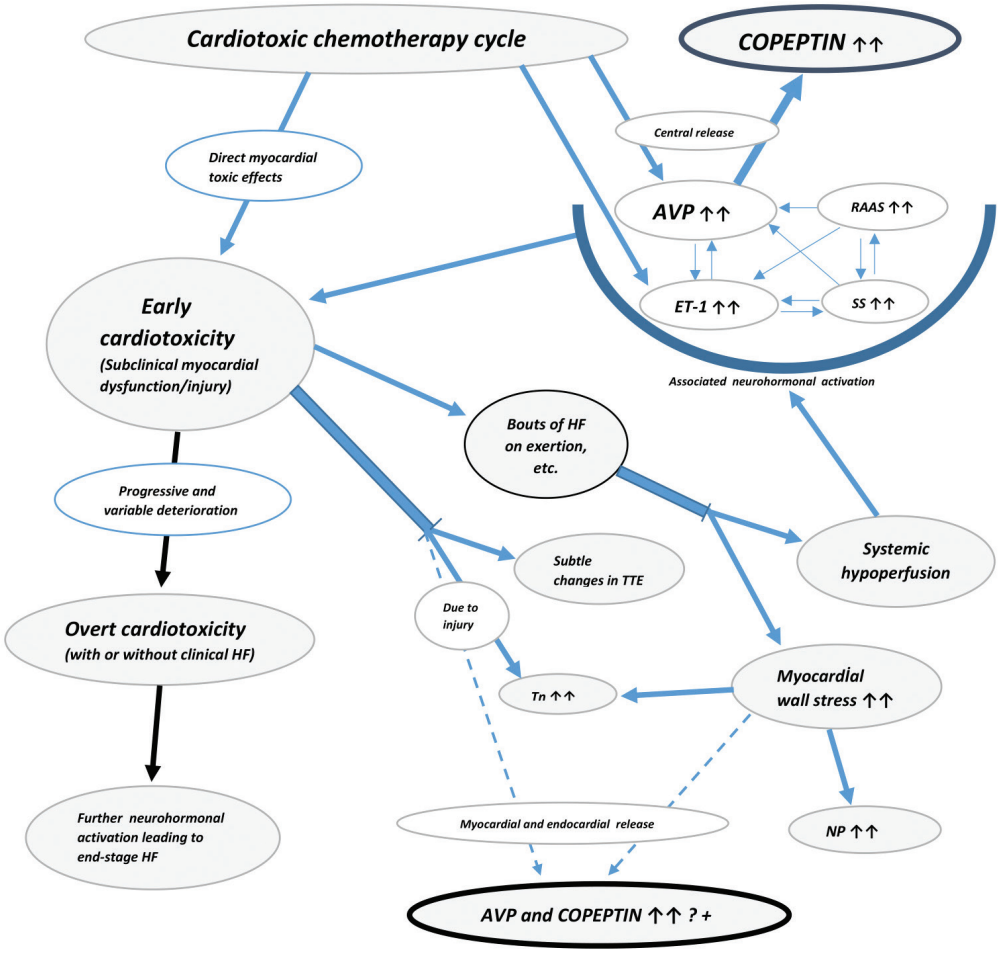

FIG. 1. Pathophysiological implications of serum copeptin and associated neurohormones in the setting of early cardiotoxicity

cardiotoxicity (based on an integrated evaluation of conventional markers) might strongly improve diagnostic power in the detection of early cardiotoxicity in clinical practice. Moreover, a significant elevation of copeptin levels in this setting might also signify the potential risk for rapid progression to overt myocardial dysfunction, warranting the use of preventive agents (RAAS and ß blockers[1,11,15]) at their maximum tolerable doses (with gradual uptitration) and the consideration of AVP and/or ET-1 antagonism (such as vaptans and bosentan). This finding also indicated the need for urgent oncology counseling for the consideration of changes in chemotherapy protocols whenever appropriate (even in the absence of overt cardiotoxicity presenting with low LVEF values). The absence of significant copeptin elevation in patients with a high likelihood of early cardiotoxicity might signify a relatively mild form of early cardiotoxicity and associated subclinical myocardial dysfunction (usually suggesting no significant involvement of AVP axis in the pathogenesis and the absence of intermittent severe systemic hypoperfusion on exertion) that potentially warrant relatively low doses of conventional preventive agents in these patients.

Conversely, in patients considered to be unlikely or lowly likely to suffer early cardiotoxicity (based on an integrated evaluation of conventional markers and tools), significant and persistent copeptin elevation following the chemotherapy cycle potentially denote a substantial risk for imminent (but not existing) early cardiotoxicity that might warrant the frequent evaluation of conventional markers (Tn-I and echocardiographic changes including strain rate) and the potential consideration of AVP and/or ET-1 antagonism (as primary prevention strategies) to preclude the evolution of early cardiotoxicity. Given that copeptin has high sensitivity,[20,21,24] the absence of copeptin elevation in this setting might safely and reliably rule-out existing and imminent early cardiotoxicity with an extremely high negative predictive value. Figure 2 demonstrates a practical algorithm for the clinical use of serum copeptin as an adjunctive guide to the detection, risk stratification, and management of early cardiotoxicity.

Other potential causes of copeptin elevation, including infections, dehydration,[20] and cancer-related complications associated with substantial stress response, should also be taken into account and

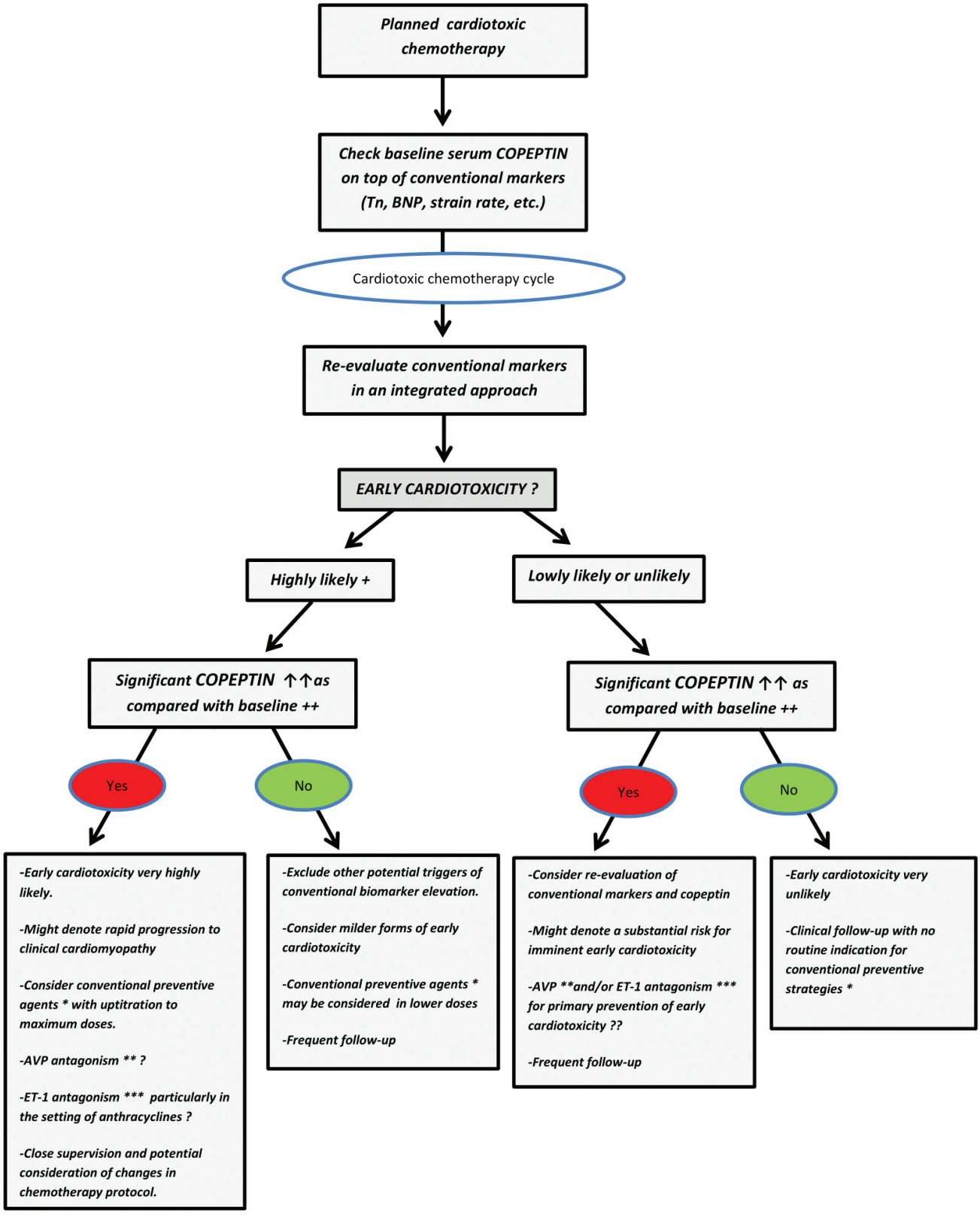

FIG. 2. Proposed algorithm for the practical use of serum copeptin as an adjunctive guide to the detection, risk stratification, and management of early cardiotoxicity

managed accordingly before the integration of serum copeptin into the clinical evaluation of early cardiotoxicity. Even though the issue of how and when to analyze conventional serum biomarkers following chemotherapy appears to be well defined in clinical studies,[12,14] the temporal changes of serum copeptin levels following a cardiotoxic chemotherapy cycle still need to be established to determine the most proper timing of serum copeptin analysis in this setting. In a manner similar to the setting of conventional biomarkers[12] the implications of persistent copeptin elevation (as determined by more than 1 sampling on consecutive days or weeks) might be stronger and clinically more relevant compared with those of transient copeptin elevation. Future studies are strongly warranted to determine the quantitative (including percent or absolute changes) and temporal definitions of critical copeptin changes following a specific cardiotoxic chemotherapy cycle. Finally, the cost-effectiveness of this biomarker remains to be established in the setting of cardiooncology practice. Nevertheless, copeptin has been reported as a cost-effective marker in a variety of conditions, particularly in combination with other biomarkers.[82]

In conclusion, Despite major advances in cancer management strategies, cardiotoxicity associated with certain chemotherapeutic regimens remains a significant therapeutic concern due to its unfavorable prognosis in the clinical setting. The proper detection of this phenomenon in its early stages and the subsequent initiation of preventive strategies significantly improve the prognosis in cancer survivors. Current diagnostic strategies (even in an integrated approach) have significant limitations, leading to mismanagement in some patients. Hence, further strategies in this setting are needed.

In addition to its specific clinical implications in patients with cancer (such as evaluation of SIADH and endogenous stress response), copeptin (the surrogate neurohormone of the AVP axis with multifaceted features) serves as an adjunctive tool for the detection of early cardiotoxicity largely owing to the pathophysiological implications of enhanced AVP actions and associated neurohormones (including ET-1) in the setting of chemotherapy-related HF. The evaluation of serum copeptin might allow the risk stratification of early cardiotoxicity and thus guide the therapeutic strategy, including the optimization of conventional preventive strategies and the consideration of further therapeutic options, such as AVP and ET-1 antagonism, in certain settings. However, the clinical and practical implications of AVP axis (and value of serum copeptin) and the potential benefit of associated therapeutic options (such as AVP antagonism) in the setting of early cardiotoxicity remain to be established through further clinical studies.

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