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Role of Corin in Cardiovascular Disease

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ARTICLE INFO

Article history:
Submitted: 19. 5. 2023
Accepted: 20. 6. 2023
Available online: 7. 12. 2023

Klíčová slova:
Corin
Hypertenze
Kardiovaskulární onemocnění
Srdeční selhání

SOUHRN

Transmembránová serinová proteáza II. typu corin, která se vyskytuje ve významném množství v srdci, aktivuje natriuretické peptidy. Do oběhu je corin uvolňován z myocytů. Cirkulující solubilní corin je spojen s hypertenzí, srdečním selháním, infarktem myokardu, preeklampsií i s cévními mozkovými příhodami. Naše výsledky naznačují, že solubilní corin může fungovat jako senzitivní a specifický biomarker predikující riziko rozvoje kardiovaskulárních onemocnění (KVO). Cirkulující solubilní corin lze bohužel obtížně použít v klinické praxi. Tento přehled shrnuje výsledky nejnovějších studií zkoumajících souvislost mezi corinem a KVO a naznačuje směry dalšího výzkumu s cílem zpřesnit predikci rizika, prognózu a farmakoterapii KVO a podpořit jeho rutinní stanovování v rámci laboratorního vyšetření.

Keywords:
Cardiovascular disease
Corin
Heart failure
Hypertension

ABSTRACT

Corin, a type II transmembrane serine protease present in significant amounts in the heart, activates natriuretic peptides. Corin enters the circulation from myocytes. Hypertension, heart failure, myocardial infarction, preeclampsia, and stroke are linked to circulating soluble corin. Our results suggest that circulating soluble corin may be a sensitive and specific cardiovascular disease (CVD) risk and predictive biomarker. Unfortunately, circulating soluble corin is difficult to use clinically. This review summarizes recent corin and CVD studies and suggests future corin research to improve risk prediction, prognosis, and medical treatment of CVDs and encourage its use as a regular laboratory test.

Introduction

Corin, a newly identified cardiac transmembrane serine protease, stimulates atrial natriuretic peptide (ANP).[1] This protease controls the heart and blood pressure.[1] Brain, kidney, pregnant uterus, and bone express corin.[2,3] Cardiovascular disease (CVD) animal models alter corin expression.[4,5] In various CVD studies, serum or plasma-soluble corin concentrations were assessed. This protease may be a biomarker since blood-soluble corin has been connected to CVD risk and prognosis.

Corin's clinical use is difficult. Unknown processes relate CVDs to circulating soluble corin. Most case-control and nested cross-sectional studies cannot relate corin to CVDs. Circulating soluble corin differs from tissue corin. Unknown. Most CV epidemiology studies have only measured soluble corin levels, not activity. Examine the overall population's demographics before employing circulating soluble corin as a biomarker. Corin is unrelated to several demographic parameters.[5]

Corin reviews have examined myocardial protease structure, function, and control in hypertension and heart failure. Hypertension, heart failure, myocardial infarction (MI), pregnancy, and stroke have been associated to circulating soluble corin levels. We analyze all data on circulating soluble corin and CVDs to determine its biomarker potential. Population-based study suggests *CORIN* gene mutations may cause CVD. We discuss soluble corin's structure, function, and measurement in circulation. This review emphasizes present issues and suggests future research to use corin in risk assessment, prognosis, and CVD treatment.

Corin structure

The 22-exon *CORIN* gene covers >200 kb on chromosome 4 in region p12–13. Corin domain boundaries match gene intron-exon junctions. Corin, a 1042-amino-acid serine protease, contains a TM domain, an N-terminal cytoplasmic tail, and numerous extracellular domains. Extracellular domains include one scavenger and a C-terminal trypsin-like protease.[6]

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DOI: 10.33678/cor.2023.055

Please cite this article as: Askin L, Poyraz F. Role of Corin in Cardiovascular Disease. Cor Vasa 2023;65:856–861.

The activation of corin

The human corin protein starts out as an inactive zymogen that needs to be cut at Arg801-Ile802 in order to work. The protease domain alters during cleavage to activate. The precursor peptide remains attached to the active corin fragment through a disulfide bond after the 801 arginine (Arg) and 802 isoleucine (Ile) cleavages (SeS). Single-chain Corin is inactive. Mutation at R801A, the conserved activation cleavage site, abolishes corin's function, proving that activation is important.[7]

The biological function of corin

Corin stimulates ANP and BNP (Fig. 1).[1] ANP and BNP regulate fluid and blood pressure.[8] Corin stimulates cell-surface natriuretic peptides during cardiomyocyte secretion. *CORIN* gene-knockout mice have no enzymes to activate pro-ANP to ANP after intravenous soluble corin.[4] Corin cleaves pro-ANP and activates pro-BNP.[1,2] Pro-ANP activation is more efficient and sequence-specific. Figure 1 depicts the biological role of corin.

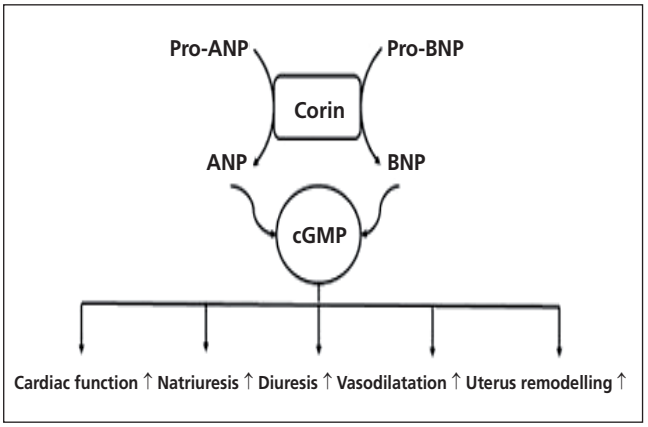

Fig. 1 – Biological role of corin. Corin can convert pro-ANP and pro--BNP to their active forms (ANP and BNP). The binding of ANP and BNP to the natriuretic peptide receptor promotes the synthesis of intracellular cyclic guanosine monophosphate (cGMP). This process can improve cardiac function and result in natriuresis, diuresis, vasodilatation, and uterus remodelling. Adapted from: Yu R, et al. Clinica Chimica Acta 2018;485:106–112.

Corin structure and function

Auto-cleavage and metalloproteinase-mediated hydrolysis remove cardiomyocyte-expressed corin.[9] Pathological or physiological conditions activate type II transmembrane serine proteases.[10,11] Tissue-vasculature-soluble corin may circulate.[2] Cell culture uses numerous soluble corins. Western blot and immunoprecipitation revealed 100-, 160-, and 180-kDa soluble corin fragments in transfected HEK 293 cells and HL-1 cardiomyocytes. Conditioned media have three activated corin-soluble fragments.[9] The 180-kDa soluble corin fragment from ADAM10 fills most extracellular space. Corin autocleavage at Arg-164 in the frizzled-1 domain creates the 160-kDa soluble corin fragment, whereas Arg427 in the LDLR-5 domain produces the 100-kDa fragment.

In transfection experiments,[7] soluble corin enzymes that don't have a transmembrane domain may also be able to handle pro-ANP. Plasma-free soluble corin processes the natriuretic peptide.[7] The 180-kDa soluble corin fragment seems to handle most natriuretic peptides. Inactive soluble corin fragments are 100- and 160-kDa.[9] The LDLR repeats and frizzled-1 domain are required to metabolize natriuretic peptides, but Corin's transmembrane domain is not.[12]

Corin measurement

Heparin-treated plasma had a soluble corin content equivalent to serum but was higher than sodium citrate or EDTA-treated plasma. EDTA- or sodium citrate-treated serum or plasma did not diminish corin levels after three freeze-thaw cycles. Sodium citrate and EDTA are better plasma corin quantification anticoagulants than heparin. Circulating corin may be a superior CVD biomarker than other peptides due to its stability.[13]

Corin and cardiovascular disease

Hypertension

Salt-water imbalance elevates blood pressure. Vasodilating, diuretic, and natriuretic peptides regulate the salt and water balance.[14] Corin-deficient animals gained weight and developed hypertension. Wang et al.[15] found that the CORIN variant allele (T555I/Q568P) defectively activated natriuretic peptides. Dries et al.[16] reported hypertension in 10–12% of African-Americans with this *CORIN* variant allele. Dong et al.[17] found a novel *CORIN* gene mutation in exon 12 in a Chinese hypertensive family with high systolic and diastolic blood pressure. Zhang et al.[18] discovered a hypertensive-specific *CORIN* gene exon 1 insertion variation. Corin protein structure and function change in vivo. *CORIN* gene mutations cause hypertension.

A 2498-person cross-sectional investigation found greater serum corin levels in hypertensives.[19] Following multivariate correction, higher serum corin increased hypertension risk. As the research was cross-sectional, the authors concluded that high blood soluble corin levels may be a risk factor or marker for hypertension. Hypertension promotes natriuretic peptides by increasing serum corin. Zhang et al.[20] support this idea. Short-term high-salt diets boost corin levels to manage salt and water balance in humans and animals. 391 hypertensives and 264 controls had reduced plasma soluble corin levels.[21] These data show circulating soluble corin may be a hypertension biomarker.

Other heart disease

Several studies on heart disease have examined the corin protein, which maintains cardiac function. Wang et al.[22] created a *CORIN* variant allele (T555I/Q568P) in transgenic mice with elevated heart pro-ANP and cardiac hy-

pertrophy. African-Americans with this *CORIN* mutation may develop heart disease and die or be hospitalized.[23] Ibebuogu et al.[24] and Peleg et al.[25] showed reduced plasma corin levels in heart failure and coronary syndrome patients. Another study of 484 heart failure patients and 484 healthy controls linked serum corin to chronic heart failure.[26] Heart failure classification lowered soluble corin levels. Healthy and acute MI (AMI) patients exhibited comparable serum corin levels. Serum corin concentrations in 856 patients and 856 healthy participants were considerably lower in the former and were linked with MI in men and women.[27] Chen et al. discovered atrial fibrillation-associated plasma corin levels in 141 patients and 127 controls.[28]

Soluble corin impacts the prognosis of heart disease. Barnet et al.[29] found that 99 coronary artery bypass graft patients with a larger relative plasma corin reduction from baseline had surgical heart failure at 60 months. Feistritzer et al.[30] demonstrated that 48-h plasma corin levels after acute ST-segment elevation MI (STEMI) predicted 4-month infarct size. Decreased plasma soluble corin predicted poor 5-year survival in a large prospective cohort of 1382 MI patients.[31] Serum-soluble corin may suggest cardiac disease. Corin overexpression improves heart function and longevity in dilated cardiomyopathy mice.[32]

Stroke

Corin stimulates blood natriuretic peptides, which increase stroke risk.[33] Circulating soluble corin may cause stroke. 597 stroke patients (116 hemorrhagic and 481 ischemic) and 2498 healthy controls showed reduced blood soluble corin concentrations in Peng et al.;[34] decreased serum soluble corin indicated 3-month severe impairment following acute stroke.[35] These findings show circulating soluble corin may be a clinical stroke biomarker.

Preeclampsia

In situ hybridization found that pregnant mice's decidual cells had corin mRNA and that human decidual cells had a lot of corin protein. Corin mRNA and protein were found in pregnant mice and people using PCR, immunohistochemical staining, and cDNA microarray. Non-pregnant uteri exhibited low corin. Late-pregnant *CORIN* gene-deficient rats developed gestational hypertension from uterine corin protein. Pregnancy-induced hypertension patients and animals agree. Preeclampsia patients with two *CORIN* gene mutations – K317E and S472G – produced defective corin proteins in vitro. K317E suppresses corin zymogen activation, whereas S472G decreases cell surface corin.[36] CORIN gene mutations may induce pre-eclampsia.

Most case-control studies found that people with preeclampsia had higher levels of soluble corin. This suggests that high blood pressure may increase corin secretion to stop preeclampsia. Plasma corin was found to negatively affect preterm preeclampsia.[37] Cui et al. found higher plasma soluble corin levels in preeclampsia patients.[5] Liu, Zaki, and Miyazaki et al. connected high blood-soluble corin to hypertensive diseases of pregnancy.[38–40] Clinically, soluble corin may indicate preeclampsia.

Perspectives

Soluble corin may predict and prognosticate CVD. Circulating soluble corin causes CV issues via unknown mechanisms. These links complicate therapeutic circulating soluble corin testing. Here, we advise additional research. Case-control studies dominate soluble corin and CVD research. Case-control studies cannot establish causation. Circulating soluble corin may cause CV issues. Soluble corin causes CVD and needs prospective cohort research. Prospective research on abnormal soluble corin levels should prevent CVD. Soluble corin may indicate CVDs.

Soluble corin activates natriuretic peptides, causing CV problems. Soluble corin may cause CV roblems. Association and correlation statistics disprove it. Natriuretic peptide routes reduce hypertensive soluble corin.[4,14] Peng et al. found increased serum corin in hypertensives.[19] Soluble corin causes preeclampsia. Circulating soluble corin and CVD require more study. In the failing heart, corin expression increased but corin activity did not,[41] highlighting the relevance of corin activity detection for assessing the link between circulating soluble corin and CVDs. Most recent CVD investigations measured serum or plasma corin levels, not soluble corin activity. CVD research needs to evaluate soluble corin activity and quantity.

Age, race, employment, income, and marriage affect CVD.[42] Disease-related demographic variables may misrepresent the relationship between circulating soluble corin and CVDs if left untreated. Before using corin as a laboratory indicator, study its demographics. Clinical corin usage rises.[2] Soluble corin has no demographics. Population-based multivariate analysis simplifies age, sex, BMI, waist circumference, blood pressure, lipids, and glucose to predict CVD.[42] Collinearity may confuse. Many studies have examined whether other variables impact circulating soluble corin and CVDs. Confounder-prespecified subgroup analysis should explore corin's risk variable interaction.

Recent studies

Chinese people with higher baseline serum corin had a higher risk of CVD events and stroke, but not coronary heart disease. This was true even when traditional risk factors were taken into account. The mechanism by which serum corin predicts stroke requires additional study.[43] Chronic kidney disease (CKD) increases cardiac and serum corin but suppresses corin activity. Reduced PCSK6 expression may cause it.[44] The Corin-(B-type natriuretic peptide)-BNP-neprilysin (NEP) protein pathway may cause atrial fibrillation (AF)-related ischemic stroke. Corin protein gene promoter CpG methylation causes AF-associated ischemic stroke.[45] Renal corin function increases natriuresis during excessive salt ingestion in mice.[46]

Black *CORIN* gene variants did not affect NP expression, circulating NP levels, BP, or hypertension in candidate gene analysis. Underrepresented populations require more research on CV genetics.[47] NT-proANP and corin may be useful indicators for assessing target organ damage in pregnant hypertensives.[48] ANP regulates blood pressure and electrolytes. Plasma ANP reduction raises

Table 1 – The main topic points of recent studies

Reference no.	Authors	Subjects	Main theme
15	Wang et al.	Mice	A *CORIN* variant allele (T555I/Q568P) in transgenic mice with elevated heart pro-ANP and cardiac hypertrophy
16	Dries et al.	Hypertensive patients	Hypertension in 10–12% of African-Americans with this *CORIN* variant allele
28	Chen F et al.	AF patients	Atrial fibrillation-associated plasma corin levels in 141 patients and 127 controls
29	Barnet et al.	KAH patients	99 coronary artery bypass graft patients with a larger relative plasma corin reduction from baseline had surgical heart failure at 60 months
30	Feistritzer et al.	ACS patients	48-h plasma corin levels after acute ST-segment elevation myocardial infarction predicted 4-month infarct size
34	Peng et al.	Stroke patients	Circulating soluble corin may cause stroke. 597 stroke patients (116 hemorrhagic and 481 ischemic) and 2498 healthy controls showed reduced blood soluble corin concentrations.
40	Miyazaki et al.	Pregnants	Clinically, soluble corin may indicate preeclampsia
44	Yang et al.	CKD patients	Chronic kidney disease (CKD) increases cardiac and serum corin but suppresses corin activity. Reduced PCSK6 expression may cause it.
50	Wang et al.	CAD patients	Missense mutation functional testing improves rare variant association analysis. Despite substantial pathophysiology and a tentative relationship, uncommonly deleterious *CORIN* mutations or circulating corin concentrations did not enhance CVD risk.
51	Gommans et al.	HF patients	Neprilysin and corin levels predict chronic heart failure (HF) patient outcomes. Enzyme control may help to categorize chronic HF patients for personalized therapy, according to recent results.
52	Abassi et al.	Pregnants	Mesometrial triangle (MT) and placenta express corin and PCSK6. In hyperinsulinemic dams (HD) placentas, corin/PCSK6 machinery causes pregnancy-induced hypertension (PIH) and intrauterine developmental restriction.
53	Xue et al.	Rats	Corin deficits in diabetic nephropathy (DN) cause endothelial dysfunction through mitogen-activated protein kinase (MAPK) and endothelial NO synthase (eNOS) signaling and renoprotection via pro-ANP processing

CVD risk. Corin matures ANP precursors. Corin deficiency disturbs electrolyte and fluid balance and ANP synthesis. Cell surface proteolytically activated zymogen corin folding, intracellular trafficking, cell surface expression, and zymogen activation may reduce corin activity. Hypertensive corin variants limit corin action. Corin and ANP have numerous physiological functions in non-cardiac tissues.[49] Missense mutation functional testing improves rare variant association analysis. Despite substantial pathophysiology and a tentative relationship, uncommonly deleterious CORIN mutations or circulating corin concentrations did not enhance CVD risk.[50]

Neprilysin and corin levels predict chronic heart failure (HF) patient outcomes. Enzyme control may help categorize chronic HF patients for personalized therapy, according to recent results.[51] Mesometrial triangle (MT) and placenta express corin and PCSK6. In hyperinsulinemic dams (HD) placentas, corin/PCSK6 machinery causes pregnancy-induced hypertension (PIH) and intrauterine developmental restriction.[52] Corin deficits in diabetic nephropathy (DN) cause endothelial dysfunction through mitogen-activated protein kinase (MAPK) and endothelial NO synthase (eNOS) signaling and renoprotection via pro-ANP processing.[53] The main topic points of recent studies are shown in Table 1.

Conclusions

Circulating soluble corin may be a sensitive and specific marker for CVD risk prediction and prognosis, despite inconsistent data. These results suggest corin-based CVD prevention, diagnosis, therapy, and prognosis. Further prospective and in-depth research are required to address the foregoing issues and promote corin's therapeutic use.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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