



# Intérêt de la VE-cadherine soluble en tant que marqueur de dysfonction endothéliale dans le syndrome coronaire chronique

Lucie Mantes

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**HAL Id: dumas-03332460**

**<https://dumas.ccsd.cnrs.fr/dumas-03332460>**

Submitted on 30 Sep 2021

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Année : 2020

**INTEREST OF SOLUBLE VE-CADHERIN AS A MARKER OF ENDOTHELIAL  
DYSFUNCTION IN CHRONIC CORONARY SYNDROMES**

THÈSE  
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLOME D'ÉTAT

Lucie MANTES

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 09/09/2020

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## Remerciements

Merci au Pr Gérard Vanzetto de me faire l'honneur de présider le jury de cette thèse. Merci pour votre enseignement du tout premier au dernier jour de mon internat, et votre générosité dans la transmission de votre savoir.

Merci au Pr Gilles Barone-Rochette d'avoir dirigé la rédaction de cette thèse et d'avoir partagé ses idées (brillantes et parfois obscures à la fois !). Merci pour vos conseils avisés, votre réactivité et votre écoute.

Merci au Pr Laurence Bouillet d'avoir accepté de juger ce travail.

Merci au Dr Isabelle Vilgrain de m'avoir ouvert les portes de son laboratoire et donné son point de vue de chercheuse sur cette petite molécule qu'est la VE-cadherine.

Merci à Clémence pour son aide précieuse à la préparation des données de cette thèse.

Merci au Pr Ennezat de m'avoir guidé tout au long de mon parcours. Merci d'avoir partagé vos connaissances et votre analyse critique et éclairée à toute heure. Merci mille fois.

Merci à tous les médecins, infirmiers, cadres, secrétaires de cardiologie du CHU de Grenoble d'avoir accompagné mes débuts (parfois chaotiques) en tant qu'interne, Hélène, Carole, Stéphanie, Estelle, Bernard, Caroline, Muriel, Aude, Charlotte, Marion, Claire, Nicolas, Alix, Rabia, Sumaya, Aurore, Maryline, Christel, David, Hubert, Aurore, Gregory, Dimitri, Marie-Blanche, Brigitte, Anne-Fred, Annie, et tous les autres ...

Merci au Pr Defaye, Peggy, Sandrine, Florian, Adrien, Mariem, Simon et Rémi de m'avoir initié à la rythmologie. Ensemble, on formait une belle équipe.

Merci au Pr Ormezzano de m'avoir permis de présenter mon premier poster à Milan !

Merci aux pneumologues de Chambéry, Dr Kelkel, Anne, Marie, Philippe, Pauline, et Julie de m'avoir reconciliée avec la médecine quand la cardio m'en paraissait éloignée.

Merci au Pr Schwebel, Pr Terzi (vive les swan-ganz), Pierre, Anne-Sophie, Anaïs, Clara, Louis-Marie et Guillaume (merci les gars !), et mes co-internes de réa méd Mariano, Thomas, Natacha, Catherine, Manuella, Lisa et Elodie, pour leur bonne humeur inégalée !

Merci au Pr Maréchaux et toute l'équipe des explos de Saint Philibert, François, Caroline, Anne Laure, Ludovic, Alexandre, Camille, Blandine, Wassima, Clémence, Tiphaine, Nathalie, Amandine, Marie, Ingrid, merci également au Pr Graux, Nicolas, Gabin, Farid, Yves, Guillaume, Aymeric, Marie, pour votre accueil si chaleureux digne du Ch'nord, et votre patience.



Merci aux cardiologues d'Annecy, Dr Belle, Dr Desjoyaux, Nathalie, Henri, Lionel, Mathieu, Océane, Sandra, Nora, Emmanuelle, Antoine, Didier, Chrystel, Pierre, Abdel, Antoine, Corine, et les plus beaux, JB, Héloïse, Manon, Antoine et Léa, pour cette belle fin d'internat les pieds dans l'eau.

Merci à tous mes co-internes cardiologues, Lisa, Wassima, Aure Elise, Johanne, Anne, Lea, Marjorie, Antoine, Lauriane, Thomas, Victor, Elodie, Sara, Arnaud, Rémi, Antoine, Guillaume, Estelle, Lou, Laura, Charles Eric, Robin, Benjamin, pour avoir ramé à mes côtés dans cette galère !

Merci à mes parents, tout simplement les meilleurs.

Merci à mamie Arlette et papi Jean-Paul pour votre soutien indéfectible, vos bons conseils et pour m'avoir logée nourrie blanchie pendant 10 ans !

Merci à mamie Henriette et papi Henri de m'avoir rendue fière de mon travail.

Merci à ma sister Fanny de m'avoir compris quand il n'y avait rien à comprendre, et donné le courage de continuer ; et à Loïc qui la soutient dans cette tâche ardue.

Merci à Guillaume, Nathalie, Carla et Axel d'avoir été le lien avec ma famille quand j'en étais éloignée.

Merci à Marie-Claire, Christian, Thibault et Solène d'avoir pris de mes nouvelles toutes ces années.

Merci à Monique, Alain, Richard, Benoît, Tiphaine, Zoey et Maïween de m'avoir si bien accueillie dans leur famille.

Merci à Alexia d'avoir aiguillé mes premiers pas à Montpellier et aidé à survivre à une année au couvent !

Merci aux Montpellier-reines, Manon, Marie, Clémence, Sandrine, Juliette, Maëlle, Laetitia, Charlotte, et Joffrey ; et leurs petits princes Mehdi, Mehdi, Loïc, Lorenzo, Mathieu, Alex. Votre amitié est un cadeau précieux. En espérant que les vacances entre copains durent encore mille ans !

Merci à mes amies, collocs et buveuses de tisane, Schach, Sabrina et Aude, pour tous ces bons moments et ces confidences. Vous êtes exceptionnelles.

Merci aux sudistes grenoblois, Geoffroy (Merci l'artiste !), Lisa (sans oublier Leika et Ima), Loïc, Marie, Carla, Eve ; et aux moins sudistes Kash et Benji, Bébé et Coco, Sophie et Damien, Ayoub, Jules, Alison, Néral, Alex et Léo, Fanny, Noémie, Cécile, Camille, Mathilde, d'avoir égayé cet internat !

Merci à Lanciaux et la brigade du Clos, Florian, Max, Moine, Erika et Helder, Laura, Camille x2, Thomas, Adrien, pour les gueuletons et les soirées fléchettes !

Merci aux Lindy-Hopers d'avoir animé les soirées grenobloises avec quelques pas de danse !

Merci aux runners lillois du mardi soir pour les bains de boue et la petite bière qui s'en suit, et à Loïc de m'avoir attendue.

Merci à Audrey et JB, mes champions de F1.

Merci à mes amis lozériens, Hugues et Nana et autres caussenards, pour m'avoir remis les pieds sur terre et rappelé les fondamentaux lors de mes retours au pays.

A Max

**Merci à tous et à toutes d'avoir partagé les bons moments comme les mauvais, et de m'avoir tant appris.**

## Abstract

**Background.** - Endothelial dysfunction (ED) is implicated in the process of atherogenesis. VE-cadherin is a specific component of adherens junctions attaching vascular endothelial cells together and to the cytoskeleton. Soluble VE-cadherin (sVE-cadherin) level, the result from the ectodomain shedding in the circulation, has been linked to vascular damage in various diseases.

**Aim.** - Evaluate sVE-cadherin as a marker of ED in the field of chronic coronary syndromes (CCS).

**Methods.** - This prospective exploratory study included 33 patients addressed for coronary angiography. Macroscopic evaluation of the coronary tree in angiography (Gensini score) and functional assessment of microcirculation using a pressure – temperature guide wire (coronary flow reserve (CFR) and index of microvascular resistance (IMR)) or TIMI frame count (TFC) were achieved. Blood samples for sVE-cadherin quantitative dosage using ELISA were available for all patients, and for 96 blood donors.

**Results.** - Mean sVE-cadherin level is significantly higher in the study group compared to the control group ( $1201.7 \pm 305.2$  ng/ml vs  $730.9 \pm 181.8$  ng/ml,  $p < 0.001$ ). sVE-cadherin level wasn't associated with the severity of atherosclerotic burden evaluated by Gensini score ( $r = -0.25$ ,  $p = 0.16$ ). No correlation was found between sVE-cadherin and TFC ( $r = -0.023$ ,  $p = 0.9$ ), CFR ( $r = -0.33$ ,  $p = 0.22$ ) or the IMR ( $r = 0.15$ ,  $p = 0.57$ ).

**Conclusion.** - sVE-cadherin level, used as a specific and easily available biomarker of ED, is increased in CCS. However, it did not correlate with the usual parameters assessing atherosclerotic stenosis severity and microvascular dysfunction.

**Key words :** soluble VE-cadherin – endothelial dysfunction – atherosclerotic burden – microcirculation – chronic coronary syndromes.

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## Résumé

**Contexte.** - La dysfonction endothéliale (DE) participe au processus d'athérosclérose. La VE-cadherine est un composant des jonctions adhérentes, complexes permettant la liaison des cellules de l'endothélium vasculaire entre elles et avec le cytosquelette. Le taux de VE-cadherine soluble (sVE-cadherine), produit du clivage de son domaine extracellulaire dans la circulation sanguine, a été relié à l'altération des fonctions de l'endothélium vasculaire dans plusieurs pathologies.

**Objectif.** - Étudier la sVE-cadherine en tant que marqueur de DE dans le cadre du syndrome coronaire chronique (SCC).

**Méthodes.** - 33 patients admis pour la réalisation d'une coronarographie diagnostique ont été inclus. La procédure permettait une évaluation angiographique des lésions (Gensini score), un calcul du TIMI frame count (TFC), et la réalisation de mesures fonctionnelles de la microcirculation grâce à un guide de pression muni d'un système de thermodilution (réserve de flux coronaire (CFR) et indice de résistance microcirculatoire (IMR)). Un dosage plasmatique de la sVE-cadherine a été réalisé, ainsi que sur 96 échantillons issus de donneurs de sang.

**Résultats.** - Le taux de sVE-cadherine est significativement plus élevé chez les patients de l'étude que dans le groupe contrôle ( $1201.7 \pm 305.2$  ng/ml vs  $730.9 \pm 181.8$  ng/ml,  $p < 0.001$ ). Ce taux n'a pas été relié à la charge athérosclérotique évaluée par le score de Gensini ( $r = -0.25$ ,  $p = 0.16$ ). Il n'a pas été démontré de relation entre la sVE-cadherine et le TFC ( $r = -0.023$ ,  $p = 0.9$ ), la CFR ( $r = -0.33$ ,  $p = 0.22$ ), ni l'IMR ( $r = 0.15$ ,  $p = 0.57$ ).

**Conclusion.** - Le biomarqueur sVE-cadherine permet un accès facilité à l'évaluation de la DE. Son taux est plus élevé chez les patients présentant un SCC que chez des sujets supposés sains, mais il n'est pas corrélé à la sévérité des lésions athéromateuses ni aux paramètres évaluant la microcirculation.

**Mots clés :** VE-cadherin soluble – dysfonction endothéliale – charge athérosclérotique – microcirculation – syndrome coronaire chronique

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## Abbreviations

AJs: Adherens junctions

CAD: Coronary artery disease

CBF: Coronary blood flow

CCS: Chronic coronary syndromes

CD144-EMP: Endothelium-derived microparticles, characterised using CD144 (VE-cadherin) antibodies

CFR: Coronary flow reserve

CMD: Coronary microvascular dysfunction

CV: Cardiovascular

ELISA: Enzyme-linked immunosorbent assay

ED: Endothelial dysfunction

EFS: French Blood Establishment

FFR: Fractional flow reserve

IMR: Index of microvascular resistance

MACE: Major adverse cardiac events

MBF: Myocardial blood flow

ng/ml: nanograms per milliliter

NO: Nitric oxide

Pa: Aortic pressure

Pd: Distal coronary pressure

PCI: Percutaneous coronary intervention

SPECT: Single-photon emission computer tomography

sVE-cadherin: soluble vascular endothelial cadherin

TFC: TIMI frame count

TmnHyp: Mean transit time at hyperaemia

TmnRest: Mean transit time at rest

TNF $\alpha$ : Tumor necrosis factor  $\alpha$

VE-cadherin: Vascular endothelial cadherin

VEGF: Vascular endothelial growth factor

# **Introduction**

## **I.1. Coronary vascular system and coronary diseases**

The ageing population along with the global epidemic of diabetes and obesity due to dietary patterns and sedentary lifestyle have led to the rising burden of cardiovascular (CV) diseases. Despite the efforts in controlling the major risk factors and the improvement in the diagnostic and therapeutic modalities, cardiac morbidity and mortality still represent a major issue.

Coronary artery disease (CAD) is a pathological dynamic process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. This condition can be modified by lifestyle, pharmacological therapies, and revascularization, which result in disease stabilization or regression (1). However, patients who present with symptoms suggestive of myocardial ischaemia and abnormal non-invasive functional tests but coronary arteries that are either angiographically normal or have moderate stenoses ( $< 50\%$  coronary diameter reduction and/or preserved fractional flow reserve (FFR)), had led to the consideration of coronary microvascular dysfunction (CMD) (2,3). These patients, also labelled as having non-obstructive CAD, benefit from a systematic approach that explore microcirculatory and vasomotor disorders. CMD and obstructive CAD share some pathogenic mechanisms including smooth muscle cell dysfunction, luminal obstruction, and endothelial dysfunction (ED) (4).

By hyperglycemia and insulin resistance, diabetes mellitus is an environment prone to endothelial dysfunction, microangiopathy, atherosclerosis and thrombosis (5), leading to alterations in the vascular system that are classified as micro- and macro-vascular complications. Diabetic patients exhibit extensive and severe epicardial coronary

atherosclerosis, with specific angiographic profiles like diffuse coronary narrowing (especially in distal arteries of smaller diameter) (6) and a higher incidence of multi vessel disease (7). Besides in this population, a substantial part of symptoms and cardiac events is related to CMD which play a role in the pathophysiology of microvascular angina (8) and diabetic cardiomyopathy (9), entities defined in the absence of significant epicardial stenosis.

The coronary arterial system is split in 3 compartments depending on their vessel anatomy and function (FIGURE 1). Myocardial tissue ischaemia and supply-to-demand mismatch can be consequences of compromised vascular function at different level of the coronary arterial bed (10). Different tools have been designed to enable functional assessment of large and small coronary arteries performing cardiac catheterization.

The Gensini score have been developed in 1983 to estimate the severity of epicardial coronary atherosclerosis on angiography. This scoring system takes into consideration the degree of luminal narrowing, the significance of the lesion location, the cumulative effect of multiple obstructions, the influence of collateral arteries and the quality of distal vessels, and the myocardial function. It provides a reproducible stratification of patients according to the functional significance of their disease (11). Calculation of the Gensini score is initiated by giving points regarding the percentage of severity score of each coronary stenosis, which is then multiplied by a factor depending on its location. Finally, the Gensini score is calculated by summation of the individual coronary segment scores (FIGURE 2).

Fractional Flow Reserve (FFR) is recognized the gold standard for evaluation of clinical significance of epicardial stenoses (12). FFR is calculated by measuring the mean distal coronary pressure with a coronary pressure wire and dividing it by the mean proximal coronary pressure, measured with a guiding catheter, during maximal hyperemia (13). FFR values  $< 0.80$  have a very high specificity for identifying ischemia, while a lesion with an FFR value  $> 0.80$  is very unlikely responsible for significant ischemia (14). This functional



evaluation has implications on therapeutic decisions and is nowadays recommended before invasive percutaneous intervention on moderate stenosis (15,16).

The coronary microcirculation is a complex and heterogeneous network of small vessels representing 80% of the total myocardial vasculature. It is composed of resistive vessels characterized by a significant drop in pressure along their length and their capacity to regulate coronary blood flow. Vasomotor tone depends on blood flow and pressure at prearterioles level and responds directly to diffusible myocardial metabolites upon intramural arterioles (2).

Direct visualization of the coronary microcirculation in vivo is currently impossible. But invasive techniques available in the catheterization laboratory provide the opportunity for a comprehensive insight into the pathophysiological substrate of CMD, including the testing of impaired microcirculatory conductance in one hand and arteriolar dysregulation in the other hand.

In 1984, Hoffman describes the concept of coronary flow reserve (CFR), based on the physiological understanding that the coronary flow at rest, when the vessels have a tone, is maintained constant for a certain range of pressure (autoregulation) ; whereas the pressure-flow relationship after maximal vasodilatation is approximately straight (FIGURE 3) (17). CFR represents the available vasodilator reserve capacity of the coronary circulation. It corresponds to the magnitude of the increase in coronary flow during maximal vasodilatation (hyperemic state), which is achieved with an intracoronary or intravenous infusion of vasodilator agents (mainly adenosine), compared to flow at rest (basal state). CFR can be calculated from coronary thermodilution curves obtained by short manual injections of 3 mL of saline at room temperature at both states (18). The development of pressure-temperature guide wire that allow simultaneous measurements of FFR and CFR by thermodilution makes it a quick and safe method with no extra cost giving complementary information on the

coronary circulation (19). CFR is defined by the ratio of the mean transit time at rest [TmnRest] to the mean transit time during hyperemia [TmnHyp] (relative value, no unit) and a CFR of less than 2.0 is considered abnormal (18).

In patients with CAD, the extent of the reduction in CFR is directly related to the severity of stenosis, whereas in persons with angiographically normal arteries, flow resistance is primarily determined by the microvasculature (2). Thus, CFR provides a combined physiological measure of large- and small-vessel function, and in the absence of obstructive CAD, is a noninvasive marker of CMD (20). Other non-invasive methods assessing CFR have been developed but are not discussed here.

The index of microcirculatory resistance (IMR) represents the minimal resistance in a target coronary artery territory achieved during maximal hyperaemia, calculated during cardiac catheterization applying the thermodilution technique (21). This index is the product of the mean transit time at hyperaemia (TmnHyp) and the distal coronary pressure (Pd) measured by the pressure wire. The normal range of IMR is  $< 25$ . As IMR is derived from the pressure across the microvasculature and the peak blood flow velocity through it, IMR is independent from large vessel disease and provides a specific quantitative assessment of coronary microcirculation (22). Contrary to CFR that is dependent in part from resting flow, IMR is not affected by variations of systemic hemodynamic conditions and thus exhibits a higher reproducibility (23).

These parameters have demonstrated a strong prognostic value of CMD for major adverse cardiac events (MACE) (24,25). Low CFR among patients with no significant epicardial stenosis (preserved FFR) (25), or high IMR measured immediately after epicardial coronary revascularization by percutaneous coronary intervention (PCI), are independent predictors of long-term MACE, indicating the prognostic importance of microvascular dysfunction beyond obstructive CAD (26,27).

The TIMI Frame Count (TFC) is an alternative indirect approach that evaluates the delayed flow of angiographic contrast which reflects an increased distal coronary resistance (known as the “coronary slow flow phenomenon”). This semi-quantitative method corresponds to counting the number of cineframes required for injected contrast to first reach a standardized distal landmark in the coronary artery. It has been developed as a simple, reproducible, objective and quantitative index of coronary flow that facilitates comparisons of angiographic end points (28). On resting conditions, TFC reflects the basal tone of the small arterioles that are the major determinant of coronary vascular resistance and therefore is indicative of microvascular status (29). Because the normal frame counts for the left anterior descending (LAD) coronary artery are 1.7 times greater than the mean for the left circumflex coronary artery (LCX) and the right coronary artery (RCA), the TFC for the LAD artery were divided by 1.7 to derive the corrected TFC. A TFC > 25 is considered as pathological.

So assessment of microcirculatory conductance (the inverse of resistance) employ thermodilution method where adenosine or dipyridole are the hyperemic stimulus used to reach maximal vasodilatation in an endothelium-independent way. In contrast, the diagnosis of arteriolar dysregulation requires the assessment of endothelial function in the coronary microcirculation by selective intracoronary acetylcholine infusion, an endothelium-dependent vasodilator.

## **I.2. Endothelial dysfunction**

ED is a disease process that results in abnormal regulation of blood vessel tone and the loss of the atheroprotective properties of normal endothelium (FIGURE 4). Effectively, this pathogenic state favors genesis and progression of atherosclerosis by four key mechanisms: impairment of endothelium-related vasodilatation, induction of inflammatory reactions, hypercoagulation and propensity to thrombosis, and cellular proliferation (30) (FIGURE 5). Reduction of nitric oxide (NO) bioavailability is an early finding in atherosclerosis and is the hallmark of dysfunctional endothelium (31). An imbalance between vasodilating and vasoconstricting substances produced by and acting on endothelial cells is a common feature encountered in CV risk conditions, with decreased NO but enhanced endothelin-1 release (32).

ED has been consistently associated with common CV risk factors like dyslipidemia, hypertension, diabetes, obesity and smoking. Given its systemic nature and its sensitivity to therapeutics, it may be thought as an integrated index of all atherogenic and atheroprotective factors present in an individual. It was also found in most conditions that predict high risk of CV events like congestive heart failure (33) and erectile dysfunction (34). ED works as a mediator and independent predictor of CV events. Thus, ED reflect a vascular phenotype prone to atherogenesis, and may serve as a marker of an unfavorable CV prognosis (35).

The multifaceted aspects of ED can be approached by biochemical markers, molecular genetic tests and invasive and non-invasive tools (36).

Early coronary physiological studies demonstrated that patients with angiographically proven CAD, whether obstructive or not, display impaired flow-mediated dilation and a vasoconstrictor response to acetylcholine rather than the normal vasodilator response (37,38). Later, other studies provide evidence that diabetes mellitus may be responsible for the same

functional alterations of the coronary circulation in patients with angiographically normal coronary arteries (39). This paradoxical response to acetylcholine infusions renders it an ideal tool to identify coronary ED (40). Effectively, the vasodilator effect of acetylcholine is called endothelium-dependent as it results from endothelial cells release of factors that causes subsequent smooth muscle relaxation (41). When the endothelial function is impaired, poor NO release is overwhelmed by the direct vasoconstricting effect of acetylcholine on the vascular smooth muscle cells via stimulation of muscarinic receptors.

As pharmacologic agents require invasive administration, physical provocation tests have been developed as an alternative. The cold pressor test (CPT) is based on the sympathetic reflexogenic stimulus developed when the forearm is immersed in ice. The vasomotor response is sustained by neuro-hormonal system activation and metabolic response to NO release secondary to coronary blood flow and myocardial work increase. Since ED in coronary atherosclerosis results in a loss of the normal dilator functions, it permits vasoconstrictor responses to sympathetic stimulation (42).

Noninvasive techniques to assess peripheral endothelial function are based in the evaluation of vasomotor response to reactive hyperemia. In normal condition, vessels respond to shear stress, generally secondary to an increase in flow, by dilating. This phenomenon designated flow-mediated vasodilation (FMD) is endothelium-dependent since principally mediated by NO. The stimulus that provokes the endothelium to release NO is a brief high-flow state subsequent to cuff deflation on the arm. Vasodilatation can be evaluated by change in brachial artery diameter measured by ultra-sound scanning (43) or by digital pulsatile volume changes recorded by peripheral arterial tonometry probes (44,45).

Both epicardial and microvascular coronary ED independently predicted acute CV events (46,47) in patients with and without CAD. Correlation was also proved with ED assessed in peripheral (brachial or femoral) arteries (48,49). Detect this process even before

the first manifestations could be a great advantage, knowing that ED can be reversed by both lifestyle changes including physical exercise and pharmacological treatment (34). Thus, as it provides both functional and prognostic information and it can be sensible to the action of vasculoprotective strategies, evaluation of ED could be an interesting tool in patients follow-up (50).

Current modalities for assessing coronary artery or peripheral endothelial function however require specialized equipment, specific training and are highly operator-dependent, and thus are not applicable to large patient populations. Biological analyses of endothelial derived components potentially offer a more simplified, noninvasive measurement of this important physiologic variable that may be more generalizable in both the clinical and research arenas (36).

For example, the implication of the endothelium in coronary atherothrombosis has been studied through membrane derived microparticles, shed in bloodstream after cell activation or apoptosis. Laboratory assays were based on the detection by flow cytometry of sized below 0.5  $\mu\text{m}$  particles, and their specific endothelial origin defined by their CD144 (VE-cadherin) positivity. Circulating plasma level of endothelium-derived microparticles (CD144-EMP) reflected the degree of chemical or ischaemic endothelial cells injury caused by diabetes (51) and arterial hypertension (52) and was significantly increased in acute clinical manifestations of CAD. Plasma CD144-EMP was independently and significantly correlated to coronary blood flow response to acetylcholine in coronary artery, that define ED (53). It also independently predicted future CV events (54). This raises the possibility that plasma levels of an endothelial protein may be a biological surrogate marker of ED in vivo.

### **I.3. VE-cadherin, a marker of endothelial dysfunction**

#### **I.3.1 Endothelial organization: Adherens junctions and VE-cadherin**

Studying the structural and molecular organization of the endothelium helps in the understanding of the mechanisms involved in ED.

Endothelium refers to single-layer cells that line the interior surface of blood vessels, forming an interface between blood in the lumen and the vascular media. It acts to maintain vascular homeostasis through multiple complex interactions between endothelial cells and the bloodstream via a plethora of cell surface receptors, and between endothelial cells attached one to the other by endothelial junctions.

Endothelial cell-cell junctions, besides maintaining endothelial integrity and barrier function, act as signaling structures of tightly regulated systems, controlling the monolayer permeability, and protecting the vessels from any uncontrolled increase angiogenesis, inflammation or thrombotic reactions (55). Tight junctions and adherens junctions (AJs) differ by their transmembrane adhesive proteins composition and structure. Their key cytoplasmic-binding partners are also crucial for cellular signalization (56).

First described by Lampugnani et al. in 1992 (57), Vascular Endothelial cadherin (VE-cadherin, also designated by 7B4 antigen, Cadherin-5 or CD144 antigen), is the major transmembrane component of endothelial AJs. This intercellular adhesion molecule is exclusively expressed by endothelial cells in all types of vessels (arterial, venous and lymphatic vessels) (58).

VE-cadherin is a 140 kDa complex protein composed of an extracellular domain and a cytoplasmic tail. The first confers the capacity of endothelial cells to aggregate one to the other in an homophilic  $\text{Ca}^{2+}$ -dependent way. The second binds to proteins partners including

p120-catenin,  $\beta$ -catenin, and plakoglobin to activate intra-cellular signaling pathways and to confer strength through interaction with the actin cytoskeleton (59) (FIGURE 6).

Experiments conducted on human umbilical vein endothelial cells had demonstrated that targeting either the extracellular domain or cytoplasmic tail provokes destabilization of AJs and consequently disruption of cell–cell junctions and dissociation of VE-cadherin binding partners. Three distinct endogenous pathways that specifically involve VE-cadherin in AJs disruption are described.

### **I.3.2 Mechanisms modulating VE-cadherin expression**

#### *Tyrosine phosphorylation of AJ components*

Several soluble factors such as vascular endothelial growth factor (VEGF), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), platelet-activating factor, thrombin, and histamine provoke transient tyrosine phosphorylation of VE-cadherin (59). VEGF-induced phosphorylation also concerns VE-cadherin associated proteins,  $\beta$ -catenin, p120 and plakoglobin, while  $\alpha$ -catenin is not affected (60).

Elevated tyrosine phosphorylation levels of junction components have been related to weak junctions, enhanced motility of endothelial cell monolayers and increased vascular permeability. On the contrary, when AJs are stabilized as in confluent cells, most of the VE-cadherin loses tyrosine phosphorylation and combines with actin. These observations indicate that phosphorylation represents a dynamic regulatory process with great potential to control important cellular and tissue outcomes.

As tyrosine phosphorylation had no effect on the composition of the cadherin complex or VE-cadherin surface expression, it has been suggested that dynamic modulation of



adhesive strength could be mediated by a redistribution of cadherin binding sites within the cell surface (lateral clustering) (61).

### *VE-cadherin endocytosis*

VEGF regulates the availability of VE-cadherin at the cell surface by promoting rapid internalization of VE-cadherin in a vesicular compartment. This process involves the phosphorylation by a Src family kinase of a conserved motif within the VE-cadherin intracellular domain and the consequent recruitment of  $\beta$ -arrestin2 (62). The internalized VE-cadherin is processed through the endosome-lysosome pathway, and modulation of lysosomal degradation is used to control VE-cadherin expression (63). Endocytosis of full VE-cadherin is reversible as it can participate in intercellular contact when relocalized to the cell surface.

These data in vitro are consistent with in vivo testing of VE-cadherin phosphorylation level depending on hemodynamic factors or inflammatory mediators (64). It appears that phosphorylation primes VE-cadherin into a dynamic state that promotes, upon activation, its rapid internalization, leading to the quick and reversible opening of endothelial cells junctions and plasma leakage.

### *VE-cadherin extracellular domain cleavage*

VE-cadherin is susceptible to enzymatic proteolysis, and its exposure to a desintegrin and metalloproteinase nowadays identified as ADAM10 results in the juxta-membranous cleavage of his extracellular domain (65). The 90 kDa VE-cadherin fragment corresponding to the ectodomain release into the circulation is named soluble VE-cadherin (sVE-cadherin).

Activation of ADAM10-dependent VE-cadherin shedding contributes to the dissolution of AJs during endothelial cell activation and apoptosis, that is functionally associated with increased vascular permeability, but also modulates gap formation during leukocyte transmigration (66). ADAM10 expression is increased in advanced human atherosclerotic plaques with many infiltrating cells and a high degree of inflammation. Also, ADAM10 plays a crucial role in various mechanisms underlying angiogenic and atherosclerotic processes (67).

Potent inducers of sVE-cadherin release inflammation through TNF $\alpha$  or thrombin, or Ca<sup>2+</sup> influx. The mechanism is not completely understood. Again, Src kinase activity has been associated with VE-cadherin tyrosine phosphorylation in its cytoplasmic domain, that is thought to be an early event which precedes the cleavage of its extracellular domain (68). One hypothesis is that the covalent phosphorylation might induce a transconformation of the protein that render it more susceptible to proteolysis.

Of note, proteolytic modifications may also happen in intra-cellular components, leading to cadherin-catenin complex disruption. Caspase-mediated cleavage of  $\beta$ -catenin and plakoglobin results in loss of their ability to bind to  $\alpha$ -catenin and thus inhibits AJs interaction with the cytoskeleton. This affects their transcriptional activity and turnover (65).

### **I.3.3 sVE-cadherin in human diseases**

In pathological conditions including inflammation, malignancy, ischaemia, and atherosclerosis (69), these 3 above-mentioned pathways trigger endothelial AJs destabilization which results into loss of vascular integrity and impaired specific endothelial functions (FIGURE 7).

At the molecular level, numerous protein interaction with VE-cadherin allow constant rearrangements on endothelial organization and modulate AJ plasticity. Mutations on the molecular components of AJs and perturbations of the underlying signaling mechanisms are at the fundament of numerous human pathologies (70). As a direct consequence of AJs deterioration, the adhesion strength between adjacent cells is deleteriously affected, resulting in increased vascular permeability (71). At the organ level, inflammation-induced breakdown of the endothelial barrier translates clinically into capillary leakage and tissue edema. This mechanism is directly linked with the severity of sepsis (72) and the disease activity in rheumatoid arthritis (68).

The value of VE-cadherin in clinical research lies in its specificity for vascular endothelial cells, leading to its use as a biomarker of ED. Since it is unlikely to evaluate full VE-cadherin endocytosis or redistribution within cell membrane in clinical situations, soluble VE-cadherin (the result of VE-cadherin ectodomain shedding into the blood stream after proteolytic degradation) appears to be the easiest way to evaluate ED in vivo. Quantitative methods like western blotting and enzyme-linked immunosorbent assays (ELISA) (73, 78) were established for the measurement of sVE-cadherin levels in human sera or plasma, expanding its use to clinical studies.

To complete the work of Blaise et al. (69) with actualized data, a search was performed using the MEDLINE database in March 2020 by entering the identical keywords: ‘sVE-cadherin’ (29 papers), ‘soluble VE-cadherin’ (111 papers), ‘VE-cadherin cleavage’ (56 papers) and ‘VE-cadherin shedding’ (28 papers). Considering only clinical studies on human population, 38 papers remained of interest. The overview of clinical studies exploring sVE-cadherin in human serum as an expression of ED in the context of various diseases is presented in supplementary information.

The number of papers dealing with VE-cadherin had greatly increased in the past years, that confirm the growing interest for the subject. Nevertheless, only few studies exist on sVE-cadherin in the field of CV diseases.

### **I.3.4 sVE-cadherin in coronary artery disease**

Donners et al explored VEGF-induced VE-cadherin cleavage mediated by ADAM10, leading to increased vascular permeability and leukocyte transmigration, two important processes in angiogenesis and atherosclerosis (67). Both VEGF and ADAM10 expression had previously been associated with atherosclerosis plaque progression and neovascularization. The same mechanism could explain vascular damage following ionizing radiation exposure (74), and the increased risk of CV disease 5 years after radiotherapy.

sVE-cadherin levels are significantly higher in patients with diabetes II mellitus, and even more in diabetic patients with CAD. They were concordant with HbA1c, an index of the disease control, and with endothelin-1, used as a marker of endothelium function (75). The alteration of the blood-retinal barrier followed by macular edema in diabetic retinopathy is an example of microvasculature alteration on a hyperglycemic environment, and the leading cause of vision loss in diabetic patients. Retinal endothelium increased permeability in diabetic animals coincides with a significant upregulation in metalloproteinase activity and the disruption of the normal continuous pattern of VE-cadherin staining on the cell surface. These alterations are found in response to advanced glycation end products exposition, through increased proteolytic cleavage of VE-cadherin (76).

SVE-cadherin concentration, measured in peripheral blood and coronary sinus, is significantly higher in patients with CAD (acute or chronic phase of myocardial infarction, or angina pectoris) compared to control subjects. Moreover, plasma sVE-cadherin concentration

is correlated with atherosclerotic burden evaluated by the Gensini score, independently of the other major atherosclerotic risk factors (77).

Spread of ED functional assessment has been limited in routine practice by the additional time and cost, the poor accessibility or the lack of expertise with these techniques. Contrariwise, sVE-cadherin has the advantages of being a specific and reproducible test for endothelial function available on peripheral circulation. We aimed to study the value of sVE-cadherin as a biological marker of ED in the evaluation of CAD. We made the hypothesis that sVE-cadherin level, determined in blood samples by our laboratory ELISA, is correlated with the presence of chronic coronary syndromes. In a second part, we wanted to explore the relationship between sVE-cadherin levels and the severity of angiographic stenosis, and its correlation with parameters of microvascular dysfunction that are well established prognosis markers in CV diseases.

## **Materials and Methods**

### **II.1. Clinical study population**

Patients referred for coronary angiography at the Grenoble Alpes University Hospital were asked for inclusion in this study. The study consisted of the evaluation for the presence of human sVE-Cadherin on blood samples. Venous samples were collected before catheterization, and for some of them, renewed 24 hours later during the hospitalization (FIGURE 8).

Coronary angiography was indicated for patients with suspected CCS according to ESC Guidelines (1). Clinical scenarios encountered were patients with clinical signs or EKG modifications suggestive of myocardial ischaemia (13 patients), following acute coronary syndrome or stroke (6 patients), asymptomatic subjects in whom CAD was detected at screening (through perfusion changes on single-photon emission computer tomography (SPECT) for 10 diabetic patients, and before cardiac surgery for 6 others).

Demographic factors and key elements of the patient's history, including risk factors and medication use, were ascertained at the time of the study by patient interview and review of medical records.

Risk factors for CV disease were defined as smoking (present or past history of tobacco use), hypertension ( $> 140/90$  mm Hg or taking antihypertensive medication), dyslipidemia (low-density lipoprotein cholesterol  $> 140$  mg/dl or taking hypolipidemic drugs), and diabetes mellitus (symptoms of diabetes plus fasting plasma glucose concentration  $> 126$  mg/dl or taking medication for diabetes).

The control group consisted of 96 blood samples taken from apparently healthy volunteers into the French Blood Establishment (EFS) blood bank. No clinical data were

available for the donors used in this study. Nevertheless, the absence of relevant medical history is a prerequisite for blood donation, that's why they can be assimilated to a healthy population.

All patients agreed to blood samples and the utilization of clinical and imaging data. Written informed consent were obtained from each patient before participation to the study, which was carried out in accordance with the guidelines approved by the ethics committee of our institution (EVARESERVE clinical trial, NCT02773043).

## **II.2. Coronary angiography**

All patients underwent a quantitative coronary angiography. The approach consisted on a radial puncture, using a 6 or 5 French catheter, with infusion of 5000 U of Heparin and 5 mg of Verapamil if necessary. The coronary tree was analyzed by luminography with a conventional guidewire, and stenosis were quantified by quantitative coronary analysis. Significant stenosis was defined by a reduction on the epicardial coronary diameter  $\geq 50\%$  associated with perfusion defect on the territory on SPECT or  $\text{FFR} \leq 0.8$ .

Gensini score was used to quantify angiographic atherosclerosis (11) (FIGURE 2). TIMI frame count in the three main arteries was calculated for all patients (28).  $\text{TFC} > 25$  is associated with increased microvascular resistance. All angiograms records were reviewed in a blinded fashion by a single senior practitioner to allow the best reproducibility in Gensini score and TFC calculation.

For microvascular assessment by the thermodilution technique, a temperature-sensitive pressure guide wire (PressureWire, Certus® (Saint Jude Medical Systems)) was localized in the mid-distal segment of a single coronary artery of choice (FIGURE 9). This particular guide wire used for usual FFR evaluation is equipped with a thermistor which

allows CFR and IMR measurement at the same time. When resting conditions are reached, three consecutive bolus injections of 3 ml of room temperature saline are performed to obtain thermodilution curves and calculate the mean transit time at rest (TmnRest). Then, hyperemic state was obtained by peripheral intravenous infusions of adenosine at 140 ug/kg/mn. The guide wire is flushed and the procedure is renewed with 3 new bolus injections of 3 ml of room temperature saline to determine the mean transit time at hyperaemia (TmnHyp).

Aortic pressure (Pa) and distal coronary pressure (Pd) are recorded at all steps, by the coronarography guide wire and the pressure guide wire respectively. FFR consists on the Pd/Pa ratio at hyperaemia. Stenosis is considered significant when FFR is  $\leq 0.8$ .

CFR is defined as the ratio of coronary blood flow during maximal vasodilation (TmnHyp) divided by coronary blood flow during autoregulation (TmnRest), and  $CFR < 2$  is considered as pathological (18).

IMR is defined as  $IMR = Pd \times (1/TmnHyp)$ , with (Pd) corresponding to the mean distal coronary pressure and (TmnHyp) representing the hyperemic mean transit time (21). The formula assumes that coronary flow is equivalent to myocardial flow and that collateral flow is negligible. However, in the presence of significant epicardial stenosis, collateral flow contributes substantially to myocardial flow while coronary flow decreases. Thus, the use of IMR value derived by the formula  $Pa \times Tmn \times ([1.35 \times Pd/Pa] - 0.32)$  is recommended in cases of functionally significant stenosis (with  $FFR \leq 0.8$ ) (27). The cut-off value of IMR is 25 (FIGURE 10).

This invasive procedure including the use of endovascular guide-wires is usual for practitioners in our catheterization laboratory in the Grenoble Alpes University Hospital. The risks undertaken by the patients have not been increased by the trial procedure.



### **II.3. Soluble VE-cadherin detection in serum**

Blood samples were withdrawn by venipuncture into 5 ml tubes containing lithium heparinate and EDTA, before any mechanical intervention. For 11 patients, a second venous blood sample was also collected after the angiography procedure. All tubes were centrifuged (3000 rpm, 10 minutes at 4°C) before storage.

All aliquots of human serum samples were brought to the INSERM laboratory, stored at -80°C and kept until they were analyzed the same day to guarantee the exact same climatic processing conditions for all. As stability of sVE-cadherin in human serum is not ensured at room temperature, all samples were thawed only 5 minutes before analysis.

sVE-cadherin dosage by ELISA method and its application have been patented by INSERM and the Grenoble Alpes University Hospital (Vilgrain I, Pelletier L, Cand F. Patent application N° WO2008062314, 2008).

The assay is a sandwich enzyme immunoassay using a monoclonal antibody and an enzyme-linked polyclonal antibody specific for sVE-cadherin, as described in supplementary information (78). The patient's sera (5 µL) were diluted 1:100 dilution in 0.5% Triton X100-containing Phosphate-buffered saline. sVE-cadherin concentration values were determined using ELISA reader (Benchmark microplate reader, Bio-Rad Laboratories, Hercules, California) and compatible software (Microplate Manager 5.2, Bio-Rad). Individual serum concentrations for sVE-Cadherin are reported in ng/mL.

### **II.4. Statistical Analysis**

Continuous variables are expressed as means  $\pm$  standard deviations. Categorical variables are summarized as numbers and percentages. Patient characteristics between the two groups were compared using the Student t-test for continuous variables or a nonparametric

Mann-Whitney test in cases of non-normal distribution; and using Chi 2 test for discrete variables. Linear regression analysis was used to compare sVE-cadherin level and coronary parameters. Statistical analysis was performed using SPSS software for Windows (version 24, SPSS, Chicago, Illinois, USA). A p value  $\leq 0.05$  was considered statistically significant.

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## Results

### III.1. Baseline clinical population characteristics

The study population consisted of 33 patients with a mean age of  $65.9 \pm 11.6$ , who underwent a coronary angiography, with a majority of males (70 %).

25 (76 %) patients were diagnosed with diabetes mellitus, mostly type II. Other CV risk factors were common: 23 (70 %) suffered from hypertension, 20 (61 %) presented with dyslipidemia, 15 (45 %) had a present or past history of tobacco use, and 25 (76 %) were overweight or obese. The mean Body Mass Index was  $28.0 \pm 3.8$  kg/m<sup>2</sup>.

More than two third of the population received at least one anti-hypertensive therapy. Antihypertensive drugs included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and diuretics. 70 % of the population was treated with hypolipidemic drugs; 58 % get an anti-platelet therapy.

Coronary angiography diagnosed obstructive CAD in 19 patients (58 %). 84% of them benefit from a revascularization procedure, PCI for 11 patients (33%) and coronary-artery bypass graft (CABG) for 5 patients (15%). Medical treatment was decided for the 3 others. All surgical procedures were indicated for three vessels disease. Those with non-obstructive CAD had either no atherosclerotic lesions (5 patients) or mild-to-moderate coronary atherosclerosis (9 patients).

Taking into consideration an IMR > 25 for the evaluation of microvascular conductance impairment (and if not available, a TFC > 25), 20 patients were diagnosed with CMD. Patients were divided into 4 groups based on the angiographic findings and thermodilution results : patients with obstructive CAD alone (8 patients), patients with CMD alone (8 patients), patients with both macro- and micro-vessels impairment (12 patients) and patients with no CCS (5 patients).

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The baseline characteristics of the study population are described in TABLE 1.

No clinical characteristics nor medical history were available for the control group, constituted of apparently healthy blood donors.

### III.2. sVE-cadherin results

The mean peripheral serum concentration of sVE-cadherin was  $1201.74 \pm 305.20$  ng/ml on the study population, and  $730.86 \pm 181.83$  ng/ml in the control group. sVE-cadherin concentration was significantly higher in patients with suspected CCS, in whom performing a coronary angiography is indicated, than in supposed healthy subjects from EFS ( $p < 0.001$ ) (FIGURE 11).

Mean Gensini score was 19.5. No correlation between Gensini score ( $r = -0.25$ ,  $p = 0.16$ ) and sVE-cadherin level was found. This absence of difference was also encountered when asymptomatic subjects that underwent coronary angiography to detected CAD as screening before cardiac surgery were excluded from analysis.

For 11 patients, blood samples were collected before and after coronary procedure. Mean sVE-cadherin before catheterization was  $1248.2 \pm 426.6$  pg/ml, and mean sVE-cadherin after stent placement was  $1171 \pm 450.8$  pg/ml. Thus, there were no significant differences in sVE-cadherin expression between pre- and post-PCI ( $p = 0.6$ ).

Mean TFC was 28.0. There was no correlation between TFC and sVE-cadherin ( $r = -0.023$ ,  $p = 0.9$ ). On patients that underwent thermodilution measurements, sVE-cadherin did not show any correlation with CFR ( $r = -0.33$ ,  $p = 0.22$ ) or IMR ( $r = 0.15$ ,  $p = 0.57$ ). Differentiating the four groups of patients did no permit to highlight any correlation between sVE-cadherin level and vascular forms of coronary arterial disorder.

## Discussion

In the present study, patients admitted for suspected CCS had a significantly higher sVE-cadherin level than control subjects. Despite the fact that blood donors could present CV risk factors, we assume patients referred to our cardiology center for cardiac catheterization were at higher CV risk, considering the high proportion of diabetic patients, the fact that 36 % of patients had a positive non-invasive functional test for myocardial ischaemia and 48% of patients required coronary re-vascularization.

On the literature, there is strong evidences of the relationship between increased in sVE-cadherin levels in circulation and endothelial dysfunction (69). In the same time, ED is an early feature in the atherogenesis process, that would be detectable even before the first clinical manifestations of a systemic vascular disease appear. ED is consistently associated with the individual burden of currently known CV risk factors (34) and the prognosis of MACE (46). Thus sVE-cadherin may provide meaningful incremental risk stratification over clinical parameters.

However, sVE-cadherin levels in our study weren't associated with the extent and severity of CAD on Gensini score. Contrariwise, the correlation with atherosclerotic burden have been demonstrated independently of the other major atherosclerotic risk factors, whether with sVE-cadherin measured in peripheral blood and coronary sinus (77). Clinical characteristics in this previous study were similar from ours, except for the prevalence of diabetes mellitus that is higher in our study group (76% vs 30%).

Interestingly, sVE-cadherin level measured before and after stent placement did not show significant change. Similarly, when sVE-cadherin evaluated in acute or chronic phase of myocardial infarction and in patients with angina pectoris, the concentration was similar in

the 3 groups (77). It appears that sVE-cadherin could be related to the degree of atherosclerosis rather than the disease activity.

In the present study, we couldn't find significant correlation between sVE-cadherin levels and indices of CMD, whether it be TFC, CFR or IMR. Despite the theoretical involvement of ED at the small vessels level that account for 80% of the myocardial circulation, there was no evidence of relation between biological findings and physiological measurements of coronary reserve and microcirculation dysfunction in our patients.

One reason advocated is that the correlation can be hidden by the presence of CAD, the microcirculatory damage being exceeded by atherosclerotic load in the entire vascular bed. Also, as ED and atherosclerosis are systemic disorders and VE-cadherin is ubiquitous, peripheral blood assay may not be able to reveal a specific organ damage. More, plasma sVE-cadherin concentrations were higher in the coronary sinus than in peripheral blood samples in patients with CAD (while there was no difference in control subject) and had a stronger correlation with the Gensini score than peripheral concentration (77). This could explain the difficulty to prove a relationship between plasma sVE-cadherin level and invasive coronary measurements.

Also, we tried to link the specific biomarker of ED to CMD but the results do not fit with our hypothesis. First, microvascular dysfunction is not only the fact of ED but also implicate various pathophysiological mechanisms like impaired smooth muscle cells reactivity, microvascular spasm, sympathetic dysfunction, altered microvascular remodeling, vascular rarefaction, extramural compression, vascular wall infiltration and luminal obstruction (79). Second, parameters observed in our study can diagnose CMD through demonstration of microvascular conductance impairment. They are thus less appropriate to reflect ED than those demonstrating endothelial-dependent vasodilatation impairment using

acetylcholine-based tests. Both mechanisms are implicated in microvascular angina but cannot be assimilated (1).

Quantitative comparison of the sVE-cadherin level found in our study population to other studies results is complicated by the difference between commercially available kit and the one we used. Indeed, the ELISA designed by Vilgrain and al. in 2013 use a recombinant human glycosylated VE-cadherin of 90 kDa as a standard for the internal calibration curve (78) (that correspond to form encountered in patient blood), while standard ones are non-glycosylated. Analysis of non-glycosylated fragments reveals non-biological multimer formation which is absent from similar fragments with natural glycosylation that only form dimers in solution. This phenomenon may explain that techniques with non-glycosylated-form antibodies may recognize only a part of the total amount of the protein (80).

This ELISA test has been previously applied for prognostic evaluation of brain tumors, metastatic breast cancer and metastatic renal cell carcinoma. Here is its first application in the field of CV diseases. Even if sVE-cadherin level is thought to represent a common pathophysiologic pathway to those pathologies, comparison with oncologic cases isn't pertinent because of the biological heterogeneity of tumors receptors expression and way to grow (81), because sVE-cadherin level can be modulated by previously administrated chemotherapies (82), and its prognosis significance is dependent on specific therapeutics availability (78).

Various approaches exist to evaluate ED but measurements of coronary flows and response to endothelium-dependent vasoactive agents require invasive and time consuming techniques, non-invasive provocative maneuvers using sympathetic stimulation are less accurate (42), that why research nowadays focus on biological molecules that could give equivalent prognostic information.

Proteomics offers several advantages: proteins are effectors of biological processes and the reflect of underlying pathological state; proteins are responsive to therapeutic interventions, informing of changes in risk; and proteins are potential targets of therapies (83). However, despite their physiological relevance and their interesting prognostic value, even promising ones did not earn their place in current practice because their increase do not implicate modifications in medical care decision.

The parallel can be made with the inflammation biomarker high-sensitivity C-reactive protein (hs-CRP), which displays the same advantages and the same limits. Inflammation like ED are common processes, known to play a role in atherosclerosis but also involved in a large range of diseases at any stage. Elevated level of serum hs-CRP is significantly associated with CAD severity on coronary angiography but also to traditional risk factors (84). Hence the presence of confounding factors and the possibility of the parallel development of other pathologies causing hs-CRP increase in an human subjects make difficult the establishment of exclusive relationship. Hs-CRP actually improve CV disease risk prediction (85) enough to warrant measurement in asymptomatic adult in routine clinical practice following American guidelines (86), and even initiation of pharmacological therapy with hypolipidemic agents (87). However, the clinical significance of this reclassification is doubtful, and in practice, physicians may be more heavily convinced by findings derived from a coronary artery image (like coronary artery calcium score) rather than from a blood test (88). Finally, the multiple types of bias in publication make the magnitude of any independent association between hs-CRP and prognosis among patients with stable CAD sufficiently uncertain (89) that no clinical practice recommendations can be made on this population.

To date, despite the large variability of CV outcomes among individuals within the same risk category, recommended primary and secondary prevention measures remain standardized for all. Identify vulnerable patients who would potentially benefit from more



intensive therapies is a challenge. Technical advances in proteomics along with high throughput technologies allowed evaluation of a broader range of plasma proteins in order to build clinical and biological models that would help risk stratification (83). Biomarker research have increased dramatically over the past decade: more than 150 CV disease biomarkers have been proposed (90). Interest in these proteins rises from their pathophysiological significance in disease genesis and their easy accessibility. Yet, their use as stand-alone parameters appeared inefficient and they are more effective when mixed with other variables, that is made possible by development of extensive data collect. Combined models including multiple biomarkers and the generally available clinical characteristics provided incremental risk stratification over Framingham secondary events scale (91,92), but these models performance needs to be evaluated and validated in large cohorts. Furthermore, doubts were expressed whether newer biomarkers actually improve risk assessment enough to warrant routine measurement in clinical practice. Subjects reclassification into other risk categories based on these models is not necessarily clinically relevant, and useless if it do not result in changes in clinical management.

In a world of precision medicine, one could imagine that proteomic characterization of “healthy” or “high risk” vascular phenotypes in conjunction with machine learning would improve accuracy in CV event prediction (93). As they are quantifiable biomarkers, a potential utilization could be evaluating the impact of medical program in the optimization of global vascular health.

Therapeutic applications have also been developed. Indeed, a successful regeneration of a competent vascular endothelium is crucial to prevent the occurrence of stent restenosis. Delayed arterial healing with incomplete re-endothelialization is a major predictor of late stent thrombosis (94). Changes in stent design and coating have been made to promote endothelial functions recovery. Innovant anti-VE-cadherin antibody-coated stents, capable of

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selective recruitment of late endothelial progenitor cell, have shown promising results with accelerated re-endothelialization and reduced neointimal formation in animal models (95).

## IV.1. Limitations

The first limitation resides in the small number of patients and the monocentric nature of the study. These assays were at exploratory purpose. Further larger randomized studies are warranted to prove the pathophysiological hypothesis.

The inability to conclude at a correlation with functional measurements may arise from the high-risk level of the study population. Most of the patients suffer from diabetes that confers about a two-fold excess risk for a wide range of vascular diseases (96). Traditional CV risk factors are widely represented. Moreover, our subjects were mostly patients with symptoms or signs of ischaemic heart disease undergoing clinically indicated or imagery-driven coronary angiography (the prognostic value of myocardial perfusion scintigraphy being well established (97)). Most of them had an impaired coronary reserve according to CFR. Highlight differences and distinguish individuals within a homogeneous population is particularly difficult.

Clinical characteristics of blood donors are missing data. The groups comparability with respect to gender, age, and CV risk level is uncertain. Confounding factors may represent of major issue. In exploratory statistics, sVE-cadherin level was significantly associated with patient's age. Long-standing treatment increased vascular rigidity or decrease in endothelial cell turn-over are potential explanations to this ascertainment.

We had to face a weak consistency between the variables evaluating CMD. Definition of microvascular status was challenging when TFC and guide-wire based measurements were contradictory. In addition, thermodilution-derived indexes were not available for all patients. It compromises the accuracy of CMD diagnosis and exposes to misclassification bias.

Both cholesterol, LDL and triglyceride-rich lipoprotein lipolysis products have been associated with abnormal NO metabolism and endothelial dysfunction (98). Patients with CV diseases commonly present dyslipidemia, yet sVE-cadherin is transported by lipoproteins in plasma. The specific use of a detergent during plasma dilution has prevented interferences of lipid concentration, and plasma aspect is checked before any sVE-cadherin dosage.

Most of the patients were undertaken pharmacological treatment for dyslipidemia, hypertension and diabetes. Although the influence of drugs on endothelial function is documented (34), there are no data available about the effect of medications on sVE-cadherin level. Also, statins may interfere with sVE-cadherin concentration by lowering the circulating levels of lipoproteins.

The sVE-cadherin concentration after PCI might be altered by the injection of contrast material during the procedure, resulting in a significant change in plasma volume and viscosity. Even if transient, direct venous infusion lead to changes in global vascular volume and thus in its constituents' concentrations. In septic states where massive infusions are required, sVE-cadherin levels were adapted to serum albumin to enable a reliable comparison between healthy and critically ill patients (72). We also observed an increase in blood viscosity visible to a naked eye that remained in samples after 24h. These modifications can affect the dosage and make the comparison to previous state inappropriate.

## **Conclusion**

The role of the endothelium in the triggering and development of coronary heart diseases is well documented, and ED is an early feature in atherosclerosis. Soluble VE-cadherin level is a simple-to-perform and non-invasive reproducible test for endothelial function, available on peripheral circulation.

In the present study, we aimed to assess the utility of sVE-cadherin in chronic coronary syndromes. Consistently with previous studies, we observed an increase in sVE-cadherin level in patients with CAD, whether obstructive (significant epicardial stenosis) or non-obstructive (microcirculatory disorder). On the contrary, we could not highlight a correlation to atherosclerotic burden evaluated by Gensini score. Finally, there was no correlation between sVE-cadherin levels and functional indices reflecting coronary microvascular dysfunction. Thus, we can hypothesize sVE-cadherin is more a reflect of overall CV health and undergoing mechanisms in the atherosclerosis process than a index of extent of coronary vessels lesions.

## Tables and Figures

**TABLE 1.** Patients characteristics.

\* values are mean  $\pm$  SD.

<b>Demographics</b>	
Age, years *	65.9 $\pm$ 11.6
Male, n (%)	23 (70)
BMI, kg/m <sup>2</sup> *	28.0 (3.8)
<b>Cardiovascular risk factors</b>	
Prior or current tobacco use, n (%)	15 (45)
Hypertension, n (%)	23 (70)
Dyslipidemia, n (%)	20 (61)
Overweight or obesity, n (%)	25 (76)
Diabetes mellitus, n (%)	25 (76)
<b>Prior history</b>	
Family history, n (%)	4 (12)
POA, n (%)	3 (9)
CAD, n (%)	6 (18)
Stroke, n (%)	4 (12)
<b>Medications</b>	
ACE-I or ARB, n (%)	20 (61)
Beta blocker, n (%)	13 (39)
Diuretics, n (%)	4 (12)
Calcium channel blocker	8 (24)
Statins	23 (70)
Antiplatelet therapy	19 (58)
<b>Laboratory data</b>	
sVE-cad, ng/ml *	1201.7 $\pm$ 305.2
<b>Coronarography procedure</b>	
Coronary angiography stenosis, n (%)	19 (58)
Non significant coronary atheroma, n (%)	9 (27)
No angiographic coronary lesion, n (%)	5 (15)
3 vessels disease, n (%)	7 (21)
Revascularization, n (%)	16 (48)
PCI, n (%)	11 (33)
CABG, n (%)	5 (15)

BMI, body mass index

POA, peripheral obliterant arteriopathy

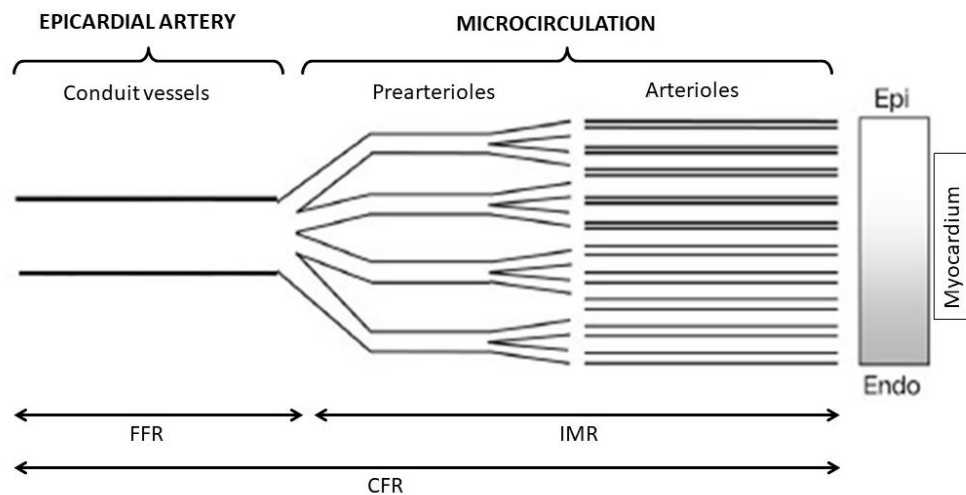
CAD, coronary artery disease

ACE-I, angiotensin-converting enzyme inhibitor

ARB, angiotensin receptor blocker

PCI, percutaneous coronary intervention

CABG, coronary artery bypass surger

**FIGURE 1. Coronary arterial system and functional evaluation (2).**

The large epicardial coronary arteries (diameter  $> 500 \mu\text{m}$  up to  $5 \text{ mm}$ ) have capacitance function and offer little resistance to coronary blood flow.

The prearterioles (diameter  $100$  to  $500 \mu\text{m}$ ) maintain a pressure at the origin of arterioles within a narrow range when coronary perfusion pressure or flow change.

The intramural arterioles (diameter  $< 100 \mu\text{m}$ ) are responsible for the matching of myocardial blood supply and oxygen consumption.

**FIGURE 2. Gensini score calculation.**

1/ A severity score is given to each coronary stenosis as follows (from 1 point for  $\leq 25\%$  narrowing to 32 points for total occlusion). Indeed, at with each step in the diameter reduction progression, the impact on flow doubles in accordance with Poiseuille's law.

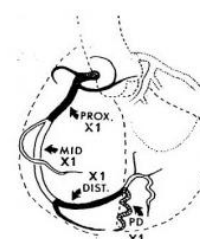
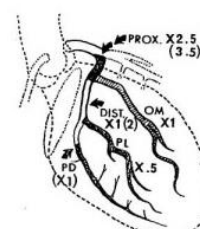
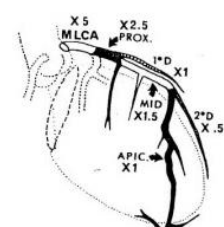
Degree of Stenosis (%)	Score
25	1
26-50	2
51-75	4
76-90	8
91-99	16
100	32

2/ Thereafter, each lesion score is multiplied by a factor that takes into account the importance of the lesion's position in the coronary circulation (see table below). The region multiplying factors were designated to express the relative amount of myocardium supplied by a diseased segment.

3/ Finally, the Gensini score was calculated by summation of the individual coronary segment scores :  $\sum (\text{Severity score} \times \text{Segment location multiplying factor})$

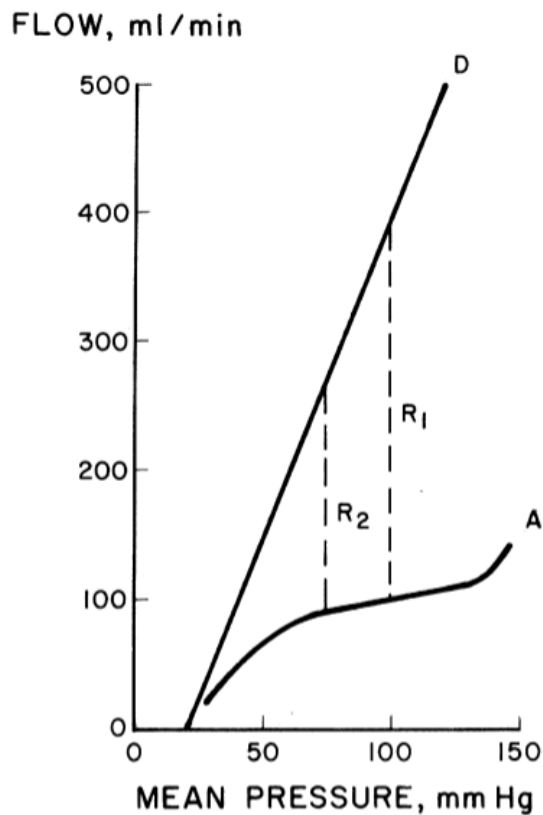
Left Coronary Artery	Multiplication Factor
Left main coronary artery (LMCA)	5
Left anterior descending artery (LAD)	
Proximal segment	2.5
Middle segment	1.5
Apical segment	1
1. Diagonal	1
2. Diagonal	0.5
Circumflex artery (Cx)	
Proximal segment	2.5 (3.5) <sup>a</sup>
Middle segment	1 (2) <sup>a</sup>
Distal segment	1 (2) <sup>a</sup>
Obtus marginal	1
Posterolateral branch	0.5
Right coronary artery (RCA)	
Proximal segment	1
Middle segment	1
Distal segment	1
Posterior descending artery (PDA)	1

<sup>a</sup> If coronary artery dominant, multiplication factor has been used number in the parenthesis.

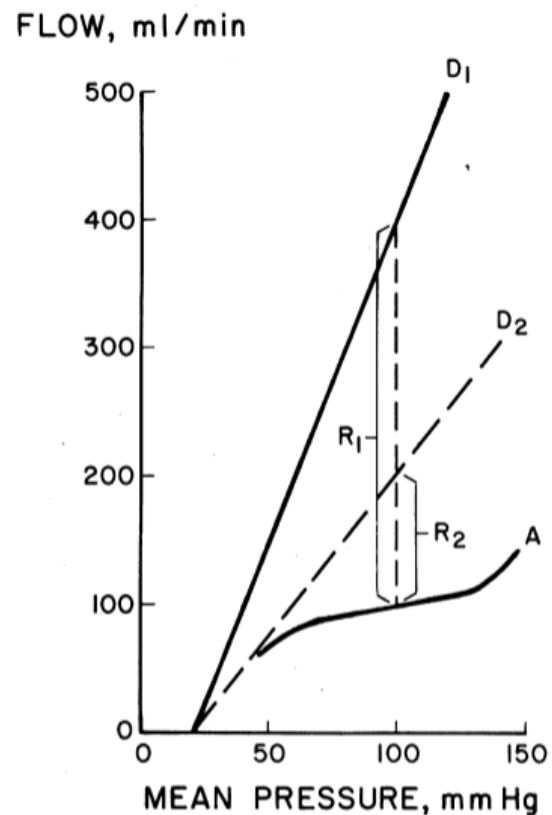


**FIGURE 3. Physiological understanding of coronary flow reserve: Diagram of pressure-flow relationships.**

**6. a.**



**6. b.**



**6. a.** Diagram of pressure-flow relationships in normal left ventricle during autoregulation (A) and maximal vasodilatation (D). R<sub>1</sub> and R<sub>2</sub> are the coronary flow reserves at mean coronary perfusing pressures of 75 and 100 mmHg when aortic pressure and heart rate are constant.

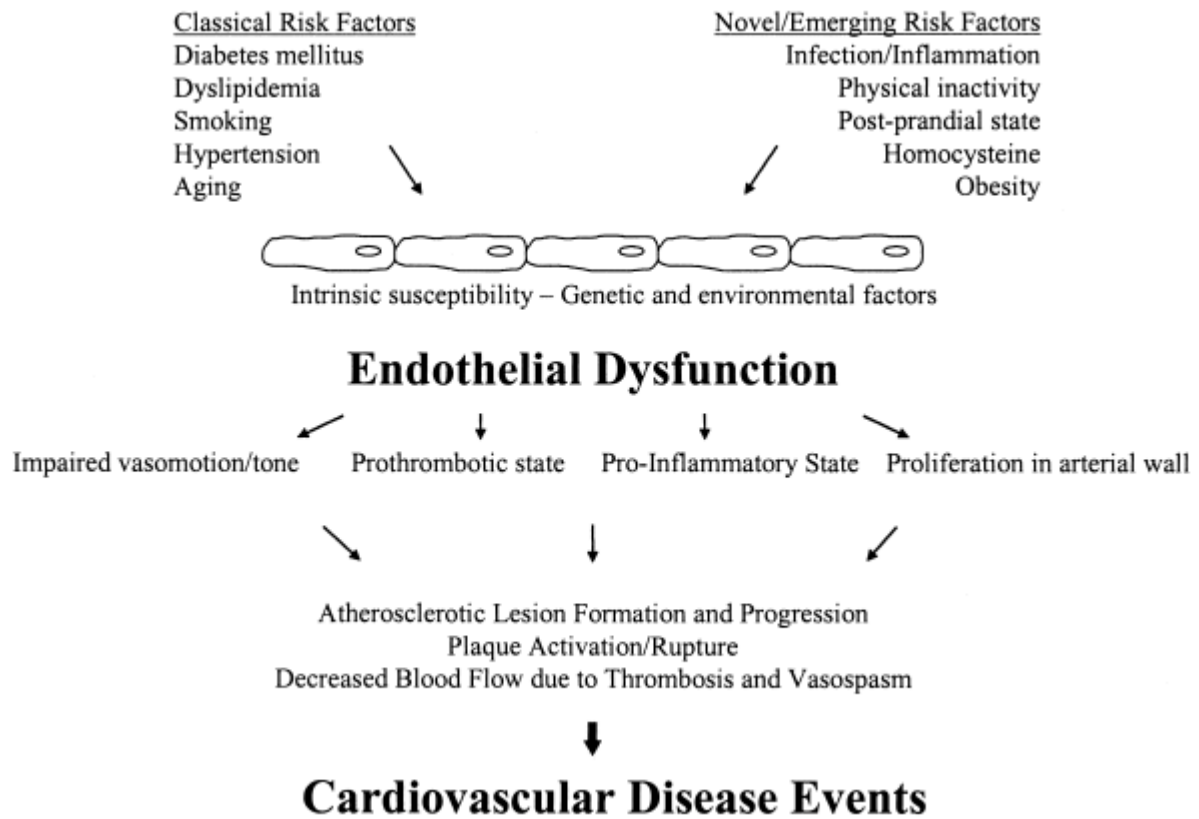
**6. b.** Diagram of pressure-flow relationships in autoregulated conditions (A) and maximally dilated vessels (D<sub>1</sub>) in a normal heart and when the pressure-flow line of maximally dilated vessels is less steep (D<sub>2</sub>). Coronary vascular reserve at any pressure is greater for the normal heart (R<sub>1</sub>) than for the heart with an increased minimal coronary vascular resistance (R<sub>2</sub>) (17).

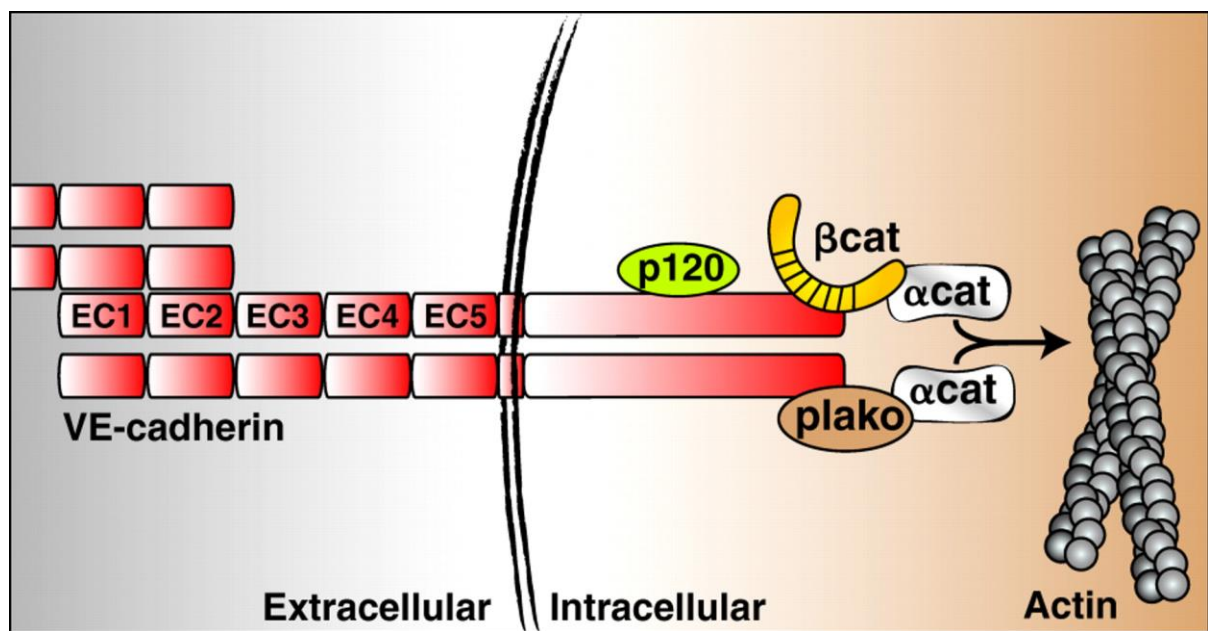


**FIGURE 4. Favorable and atheroprotective effects of the healthy endothelium (35).**

Promotion of vasodilation
Antioxidant effects
Antiinflammatory effects
Inhibition of leukocyte adhesion and migration
Inhibition of smooth muscle cell proliferation and migration
Inhibition of platelet aggregation and adhesion
Anticoagulant effects
Profibrinolytic effects

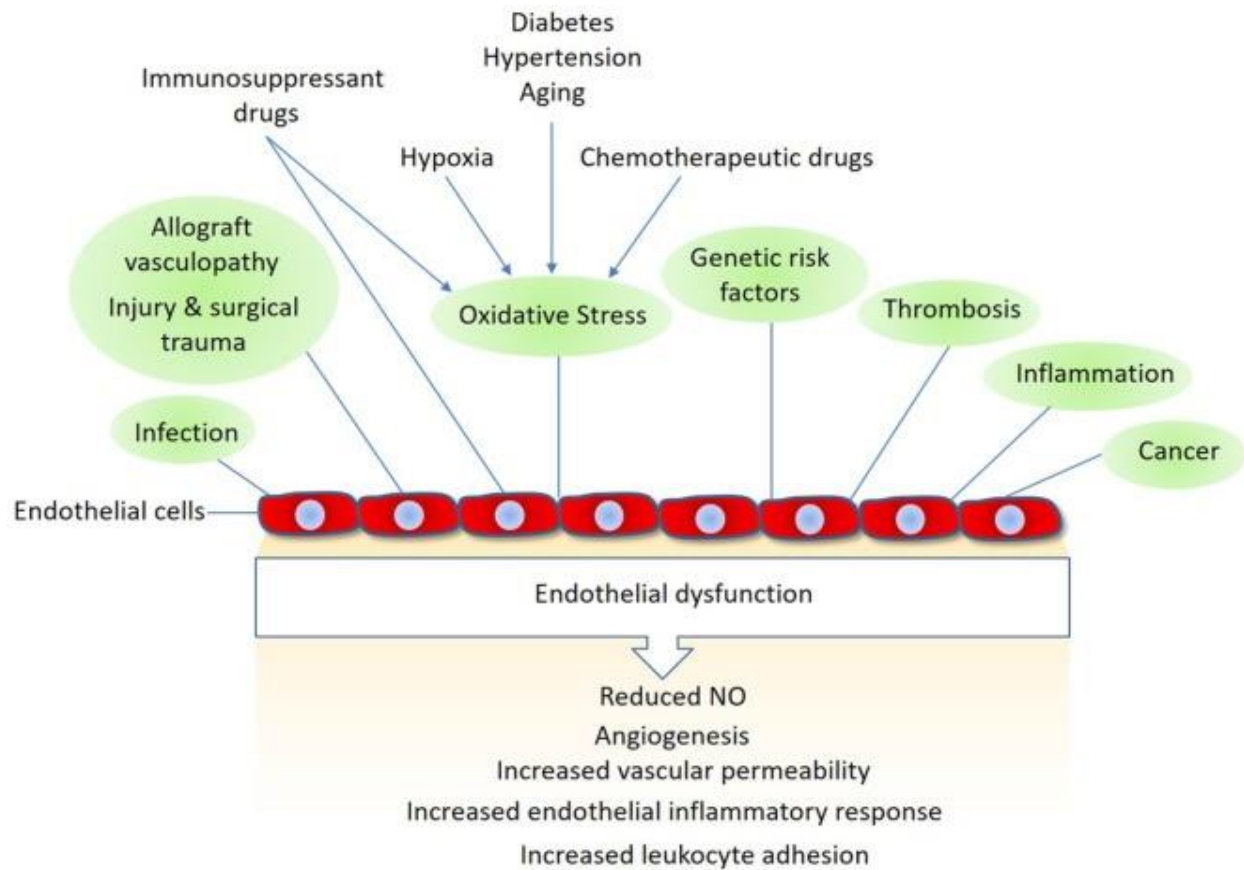
**FIGURE 5. The role of endothelial dysfunction in the pathogenesis of cardiovascular disease events (50).**



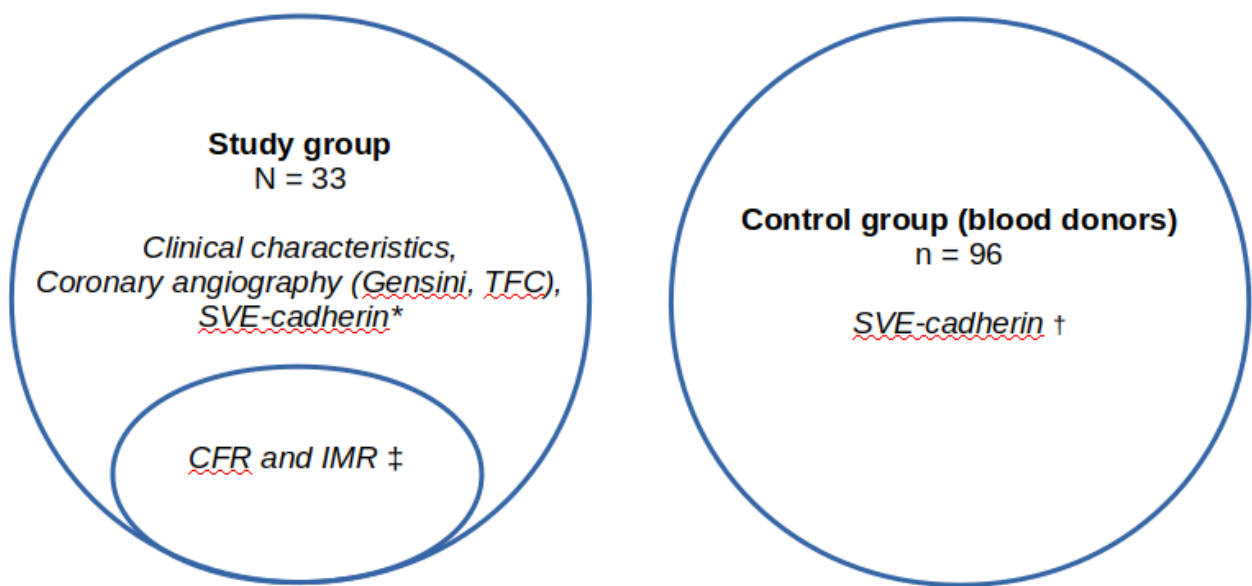
**FIGURE 6. Molecular organization of endothelial Adherens Junctions (71).**

Cadherins are single chain transmembrane glycoprotein. The extracellular domain consists of five homologous repeats of 110 residues which contain  $\text{Ca}^{2+}$  binding sequences whose depends homophilic endothelial cell-cell adhesion. The cytoplasmic tail of VE-cadherin comprises two well-characterized domains. The juxtamembrane domain binds to the catenin p120, a protein belonging to the “armadillo” family. At the carboxyl-terminal region of the cytoplasmic tail, the catenin binding domain interacts with  $\beta$ -catenin or plakoglobin. The latest interact with  $\alpha$ -catenin, that mediates the linkage of the “cadherin–catenin complex” to the actin cytoskeleton.

**FIGURE 7. Mechanisms linked to endothelial dysfunction: several key mechanisms that promote endothelial dysfunction and vascular damage are shown. Also, shown are the major endothelial responses triggered by these factors (56).**



**FIGURE 8. Study and Control groups.**

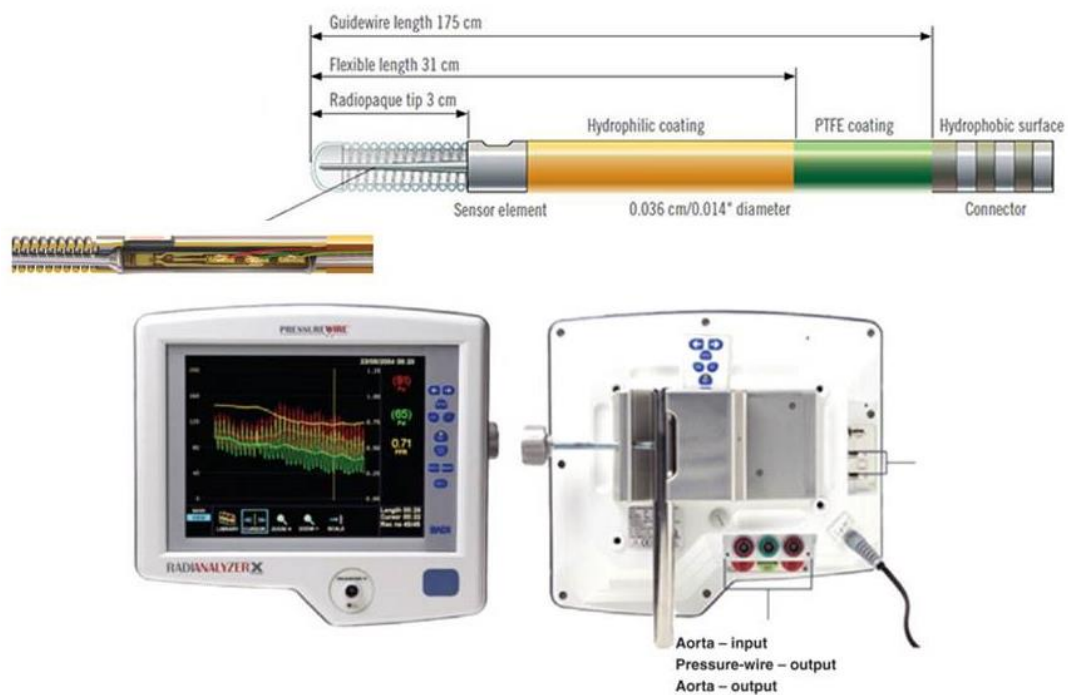


\* : Clinical characteristics, coronary angiography with Gensini score and TIMI Frame Count (TFC) calculation, sVE-cadherin level determination were available for all patient from the study group.

‡ : CFR and IMR values were available for half of the patients evaluated in catheterization laboratory.

† : Only sVE-cadherin determination was available for the control group.

**FIGURE 9. Temperature-sensitive pressure guide wire (PressureWire, Certus®, Saint Jude Medical Systems).**

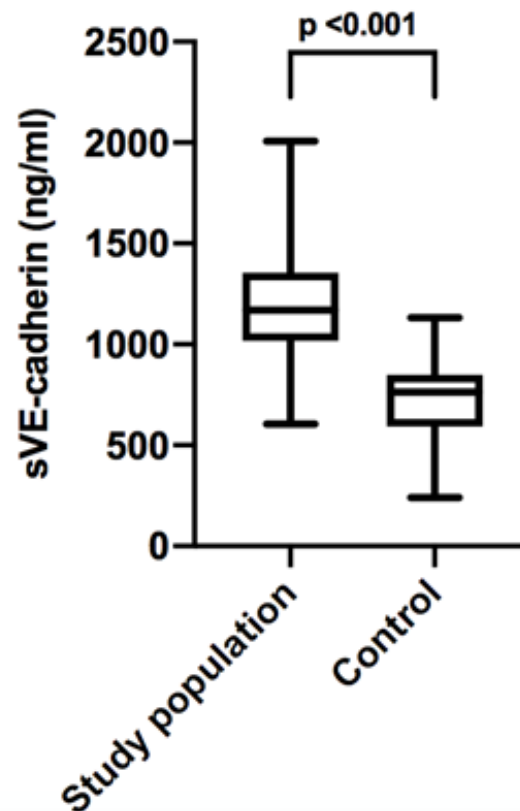


The high-definition sensor has a patented 3-in-1 functionality: pressure (FFR), flow and temperature (CFR and IMR).

**FIGURE 10. Mathematical formula for coronary physiology measurements using thermodilution method (20,22,99).**

$$\begin{aligned} \text{Absolute coronary flow} &\approx \frac{1}{T_{mn}} \\ \text{CFR} &= \frac{\text{Coronary flow at hyperemia}}{\text{Coronary flow at rest}} \approx \frac{\frac{1}{T_{mnHyp}}}{\frac{1}{T_{mnRest}}} = \frac{T_{mnRest}}{T_{mnHyp}} \\ \text{IMR} &= \frac{P_d}{\frac{1}{T_{mnHyp}}} = P_d \times T_{mnHyp}, \text{ in the absence of epicardial stenosis} \\ \text{IMR} &= P_a \times T_{mnHyp} (1,35 \times P_d / P_a - 0,32), \text{ in case of epicardial stenosis} \end{aligned}$$

Cut-off values were  $\text{FFR} \leq 0.80$  (low FFR),  $\text{CFR} \leq 2.0$  (low CFR) and  $\text{IMR} \geq 25$  (high IMR).

**FIGURE 11.** Mean sVE-cadherin level in study population and control group.

Plasma sVE-cadherin levels were significantly higher in patients with suspected chronic coronary syndrome admitted for coronary angiography compared to blood donors ( $1201.7 \pm 305.2$  ng/ml vs  $730.9 \pm 181.8$  ng/ml,  $p < 0.001$ ).



***SUPPLEMENTARY INFORMATION***

**Overview of clinical studies registered in MEDLINE database in March 2020 where soluble vascular endothelial-cadherin (sVE-cadherin) was measured in human serum.**

N°	Ref.	Year	Disease	No. of patients	Control	Results	Method used to quantify sVE-cadherin
1	77	2004	Coronary atherosclerosis	24 myocardial infarction, 26 angina pectoris, 18 old myocardial infarction	YES : 30 control patients (normal coronary angiography)	5.1 ± 2.5 ng/mL (myocardial infarction) vs 4.7 ± 2.4 ng/mL (angina pectoris) vs 4.5 ± 3.3 ng/mL (old myocardial infarction) vs 2.6 ± 2.3 ng/mL (normal coronary angiography); p < 0.001	Bender MedSystems
2	100	2006	Colorectal cancer	125 patients with colorectal cancer	YES : 16 HV	1.68 ng/mL (colorectal cancer) vs 0.42 ng/mL (HV); p < 0.00001	Bender MedSystems
3	101	2006	Multiple myeloma	46 multiple myeloma	YES : 22 HV	1.36 ± 0.55 ng/mL (multiple myeloma) vs 0.63 ± 0.56 ng/mL (HV); p < 0.005	Bender MedSystems
4	102	2008	Ovarian hyperstimulation syndrome (OHSS)	28 severe OHSS (sOHSS)	YES: 34 women undergoing controlled ovarian hyperstimulation (cOHS)	sOHSS > cOHS; p = 0.0001	Bender MedSystems
5	103	2008	Lymphoma	40 non-Hodgkin lymphoma	YES : HV (n= DM)	DM	DM
6	104	2010	Behçet disease	44 Behçet disease	YES : 53 HV	Significant difference DM	DM
7	105	2010	Sepsis	28 sepsis	YES : 13 HV	2.64 ng/mL (sepsis) vs 1.13 ng/mL (HV); p < 0.0001	Bender MedSystems
8	68	2011	Hereditary angioedema	1 before and 1 after attack	NO	NA	Western blotting analysis; patent WO 2008/062314
9	106	2012	Rheumatoid arthritis (RA)	63 RA	NO	NA	Western blotting analysis; patent WO 2008/062314
10	78	2012	Gastrointestinal cancers	35 advanced refractory gastrointestinal cancer	YES : 16 stable gastrointestinal cancers and 19 progressive disease	Not statistically significant	Bender MedSystems, Vienna, Austria
11	107	2013	Glioma	53 glioma	NO	NA (prognostic value)	ELISA VEC; patent WO 2008//062314
12	108	2013	Sepsis	20 severe sepsis or septic shock	NO	NA	Bender MedSystems
13	109	2014	Henoch-Schönlein purpura (HSP)	30 HSP, 20UV, 13 AV, 12 BD, 20 PV, 20 AD	YES : 26 HV	12.28 ± 7.06 U/mL (HSP), p = 0.001; 11.66 ± 6.98 U/mL (UV), p = 0.002; 13.42 ± 8.5 U/mL (AV), p = 0.005; 12.62 ± 7.84 U/mL (BD), p = 0.007; 7.87 ± 3.55 U/mL (PV), p = NS; 7.74 ± 2.81 U/mL (AD), p = NS; 6.92 ± 2.72 U/mL (HV), p = NA	Bender MedSystems, Vienna, Austria
14	110	2014	Sepsis	47 sepsis / 47 septic patients	YES : 25 chronic kidney	3424.1 ± 2033.0 ng/mL (sepsis),	Bender MedSystems

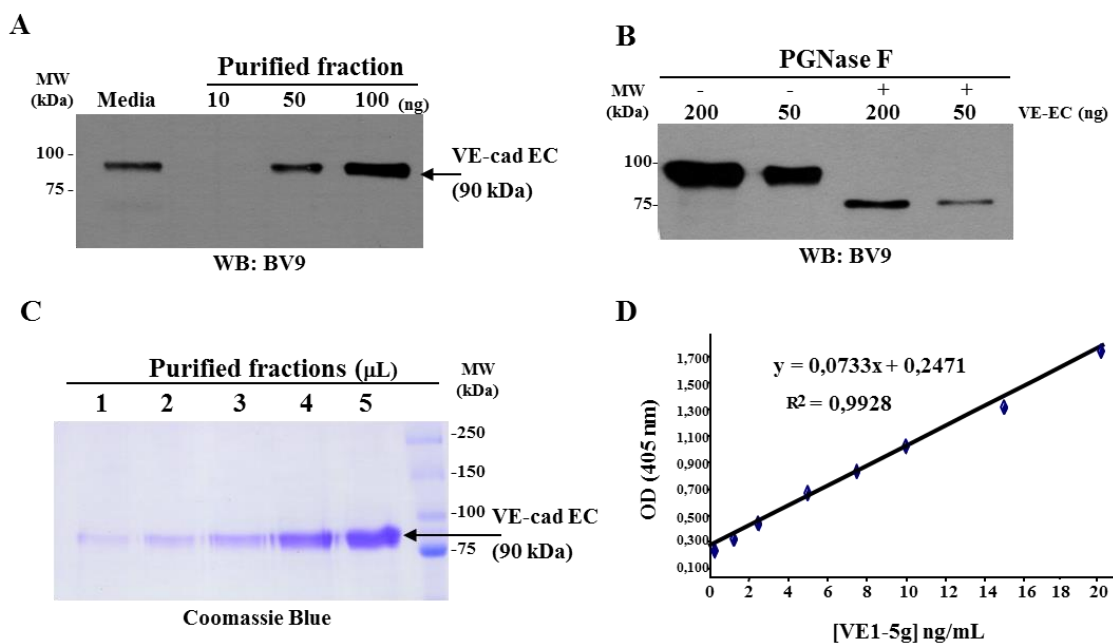
				treated by direct hemoperfusion with a polymyxin B-immobilized fiber column (DHP-PMX)	disease (CKD) / without sepsis	5862.0 ± 1521.2 ng/mL (CKD controls) ; p < 0.0001	
15	111	2014	Hemodialysis patients	10 hemodialysis patients	YES : 10 HV	1.46 ± 0.07 vs 1.25 ± 0.06 (HV) relative density units; p < 0.05	Western blotting analysis
16	112	2015	Red blood cells transfusion	58 patients with transfusion-dependant haematologic diseases	YES : 31 HV (blood donors)	2236 (1869-2984) ng/ml before RBC transfusion, 2153 (1766-3103) ng/ml 1h after RBC transfusion, 2307 (1830-3026) ng/ml 24h after RBD transfusion in patients with blood disease ; 2352 (20087-2781) ng/ml in healthy controls ; not statistically significant	ELISA, R&D Systems Europe, Ltd., Abingdon, UK
17	113	2015	Platelet transfusion	22 patients	YES : 31 HV (blood donors)	2214 (2007-2526) ng/ml before platelet transfusion, 2049 (1805-2341) ng/ml 1h after platelet transfusion, 2238 (1958-2495) ng/ml 24h after platelet transfusion in patients group (p 0.002) ; 2352 (2087-2781) ng/ml in healthy controls, not statistically significant	ELISA, R&D Systems Europe, Ltd., Abingdon, UK
18	114	2015	Human immunodeficiency virus (HIV)	67 HIV+	YES : 15 HV	DM	ELISA, R&D Systems Europe, Ltd., Abingdon, UK
19	115	2015	Out-of-hospital cardiac arrest (OHCA)	163 OHCA	NO	NA (prognostic value) 2.595 (2.303-3.174) ng/ml	ELISA, R&D Systems Europe, Ltd., Abingdon, UK
20	72	2015	Shiga toxin 2 producing Escherichia coli (STEC) infection, with or without haemolytic uraemic syndrome (HUS)	79 STEC-HUS, 77 STEC without HUS	YES : 200 control patients with diarrhea	DM, lower in STEC-HUS than STEC without HUS and control, p < 0.05	ELISA, R&D Systems, Minneapolis USA
21	116	2015	Sepsis	7 severe sepsis	YES : 11 HV	5047 ± 603 ng/mL (severe sepsis), 2609 ± 168 ng/mL (healthy) ; p ≤ 0.05	ELISA, DCADV0; R&D Systems, Wiesbaden-Nordenstadt, Germany
22	117	2016	Metabolic syndrome	240 young adults	NO	NA (correlation with MetS, obesity and HTA)	ELISA, eBioscience
23	118	2016	Post-cardiac arrest syndrome (PCAS)	163 comatose patients	NO	DM, NA (prognostic value of sVE-cad)	ELISA, R&D Systems Europe, Ltd., Abingdon, UK

24	119	2017	Subarachnoid Hemorrhage (SHA)	59 SHA patients with delayed prostacyclin infusion	YES : 30 SHAH with placebo	Not statistically significant	ELISA, eBioscience
25	81	2017	Chronic spontaneous urticaria (CSU)				DM
26	120	2017	Metastatic breast cancer (MBC)	150 patients with hormone-refractory MBC	NO	NA (prognostic value of sVE-cad)	ELISA VEC; patent WO 2008//062314
27	121	2017	Trauma	404 patients with trauma	NO	NA (prognostic value of sVE-cad)	DM
28	122	2017	Rheumatoid arthritis	48 RA treated by anti-TNF	NO	NA (correlation with inflammation / CRP levels)	ELISA
29	123	2017	Necrotising soft tissue infections (NSTI)	150 NSTI	NO	DM (protocol only)	ELISA, R&D systems
30	124	2017		15 conventional coronary artery bypass (CCAB)	YES : 15 off-pump coronary artery bypass grafting (OPCAB)		
31	125	2018	COPD	115 COPD, 36 symptomatic smokers	YES : 63 healthy smokers, 78 healthy non smokers	Significantly lower in the COPD and SS group than in the HS group	Bender MedSystems, Vienna, Austria
32	126	2018	Thoracic aorta dissection (TAD)	29 TAD patients treated with OctaplasLG®	YES : 28 TAD patients treated with fresh frozen plasma	DM (diminished increase in sVE-cadherin in OctaplasLG® group)	ELISA, R&D Systems, Minneapolis, MN
33	82	2018	Chronic venous insufficiency (CVI)	44 women with CVI	YES : 25 healthy women	39.30 (36.19-42.11) ng/ml (control), 30.34 (23.36-34.44) ng/ml (moderate CVI), 31.56 (26.31-41.90) ng/ml (severe CVI) ; p = 0.002	ELISA, R&D Systems, Minneapolis, MN
34	127	2018	Metastatic renal cell carcinoma (mRCC)	133 mRCC	YES : 96 HV	1831 ng/mL [min-max: 90-4484] (mRCC), 731.0 ng/mL [min-max: 240-1133] (HV) ; p < 0.001	ELISA VEC; patent WO 2008//062314
35	128	2019	Dengue Hemorrhagic Fever	62 DHF patients with shock	YES : 48 DHF patients without shock	Not statistically significant	ELISA, not precised
36	129	2019	Severe sepsis and acute respiratory failure	228 patients	NO	Significantly higher in patients with acute kidney injury and with greater than 2 organ failure	ELISA, R&D Systems, Minneapolis, MN, USA
37	130	2019	Severe trauma	12 patients with endotheliopathy of trauma (EOT)	YES : 12 control patients	3108 (2753 – 3984) ng/ml (EOT) ; 2843 (2464 – 3049) ng/ml (control) ; p = NS	ELISA, R&D Systems Europe, Ltd., Abingdon, UK
38	131	2020	Subarachnoid Hemorrhage (SAH)	52 patients with SAH	YES : 16 control patients	DM	ELISA, R&D Systems, Minneapolis, MN

**ELISA for soluble VE-cadherin detection in human serum (78)**

The assay is a sandwich enzyme immunoassay using a monoclonal antibody and an enzyme-linked polyclonal antibody specific for sVE-cadherin. The capture monoclonal antibody has been pre-coated onto a 96-wells microplate overnight (ON) at 4°C. After a 1h period of incubation at room temperature (RT) with 100 µL of block buffer followed by washing (3 times), 100 µL of calibration, validation and human serum samples were added. After a 2h period of incubation, unbounded substances were removed by a second washing. 100 µL of the second antibody (Anti-Cad 3 IgG) were added to the wells and after a third incubation of 1 hour followed by washing. 100 µL of a polyclonal goat anti-rabbit immunoglobulins biotinylated were added. After 1h of incubation followed by washing, 100 µL of streptavidin-alkaline phosphatase were dispensed for 30 minutes. After washing, 200 µL of the substrate (pNPP) were added. During incubation, color developed in proportion to the amount of sVE-cadherin bounded in the initial step. The color development was followed up to 30 minutes and the enzymatic reaction was stopped by the addition of NaOH 3N. The absorbance was read at 405 nm using an ELISA reader (Benchmark microplate reader, Bio-Rad Laboratories, Hercules, California) and compatible software (Microplate Manager 5.2, Bio-Rad). All the analyses were performed in duplicate. The calibration range was from 2.5 to 40.0 ng/mL. Analytical data treatment: The calculations were performed independently. Raw data (OD) measured by the plate reader were plotted against nominal standard concentrations to construct the standard calibration curves. Concentration values of unknown samples were interpolated from these curves using an unweighted linear regression of the data. A typical standard curve is presented in Supplementary Figure 1. Throughout the study, the CVs of standards were from 1.26% to 9.54%. No cross-reactivity between soluble VE-cadherin and other adhesion molecules has been found using this assay. Experiments were performed in triplicate. The patient's sera (5 µl) were diluted 1:100 dilution in 0.5% Triton X100-containing PBS. Individual serum concentrations for VE-Cadherin are reported in ng/mL.

Supplementary Figure S1: Production of human recombinant glycosylated sVE-cadherin in EBNA cells and development of standard calibration curve for ELISA quantification of sVE-cadherin in human serum.



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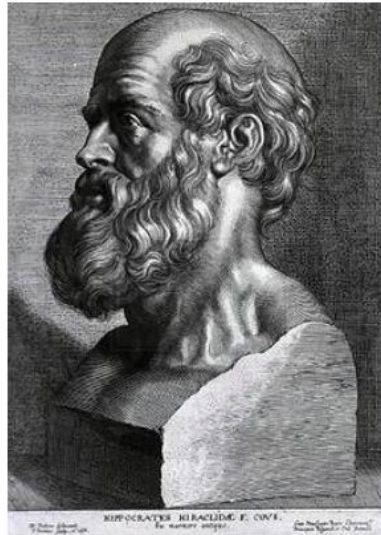
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## Serment d'Hippocrate



### **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*

**THÈSE SOUTENUE PAR :** Lucie MANTES

**TITRE :**

INTÉRÊT DE LA VE-CADHERINE SOLUBLE EN TANT QUE MARQUEUR DE  
DYSFONCTION ENDOTHÉLIALE DANS LE SYNDROME CORONAIRE CHRONIQUE

**CONCLUSION :**

**Contexte :** La dysfonction endothéliale (DE) participe au processus d'athérosclérose. La VE-cadherine est un composant des jonctions adhérentes, complexes permettant la liaison des cellules de l'endothélium vasculaire entre elles et avec le cytosquelette. Le taux de VE-cadherine soluble (sVE-cad), produit du clivage de son domaine extracellulaire dans la circulation sanguine, a été relié à la DE dans plusieurs pathologies.

**Objectif :** Étudier la sVE-cad en tant que marqueur de DE dans le cadre du syndrome coronaire chronique (SCC).

**Méthodes :** 33 patients admis pour coronarographie diagnostique ont été inclus. La procédure permettait une évaluation angiographique des lésions (Gensini score), un calcul du TIMI frame count (TFC), et la réalisation de mesures fonctionnelles de la microcirculation par méthode de thermodilution (réserve de flux coronaire (CFR) et indice de résistance microcirculatoire (IMR)). Un dosage plasmatique de la sVE-cad a été réalisé, ainsi que sur 96 échantillons issus de donneurs de sang.

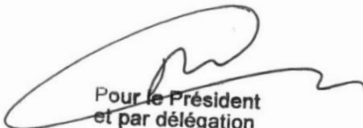
**Résultats :** Le taux de sVE-cad est significativement plus élevé chez les patients de l'étude que dans le groupe contrôle ( $1201.7 \pm 305.2$  ng/ml vs  $730.9 \pm 181.8$  ng/ml,  $p < 0.001$ ). Ce taux n'a pas été relié à la charge athérosclérotique sur le score de Gensini ( $r = -0.25$ ,  $p = 0.16$ ). Il n'a pas été démontré de relation entre la sVE-cad et le TFC ( $r = -0.023$ ,  $p = 0.9$ ), la CFR ( $r = -0.33$ ,  $p = 0.22$ ), ni l'IMR ( $r = 0.15$ ,  $p = 0.57$ ).

**Conclusion :** Le biomarqueur sVE-cad permet un accès facilité à l'évaluation de la DE. Son taux est plus élevé chez les patients présentant un SCC, mais il n'est pas corrélé à la sévérité des lésions athéromateuses ni aux paramètres évaluant la microcirculation.

**VU ET PERMIS D'IMPRIMER**

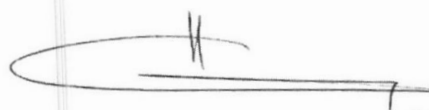
Grenoble, le : 25/10/81

**LE DOYEN**

  
Pour le Président  
et par délégation  
Le Doyen de Médecine  
Pr. Patrice MORAND

**Pr. Patrice MORAND**

**LE PRÉSIDENT DE LA THÈSE**



**Pr. Gérald VANZETTO**