Cardiovascular Continuum 25 years – The Evolution of an Etiopathophysiology Model

Evandro Tinoco Mesquita, Amanda Vanessa Demarchi, Dezirrê dos Santos Bitencourt, Patricia Elaine de Azevedo Machado, Paula Meneguini Badran, Renata Gudergues Pereira de Almeida, Antonio José Lagoeiro Jorge

Università Federal Fluminense – Hospital Universitário Antônio Pedro – Departamento de Medicina Clínica – Niterói, RJ – Brazil

Abstract

The concept of cardiovascular continuum was devised by Dzau and Braunwald and spread among cardiologists as an etiopathophysiology model that directs the development of interventionist measures in the prevention of cardiovascular diseases. After a workshop held in 1989, it was possible to gather resolved and unresolved issues about factors related to cardiovascular therapy and protection, resulting in the first publication by Dzau and Braunwald, in 1991. Progress in the studies of molecular and cellular biology allowed understanding the role of endothelial dysfunction in oxidative stress and nitric oxide in coronary artery atherosclerosis (CAA), awarding Nobel Prize to authors Ferid Murad, Robert Furchgott and Louis Ignarro. In 2006, a second publication, also led by Dzau, consolidated the classic model of cardiovascular continuum, in which risk factors for CAA are associated and trigger a progressive cascade of events leading to the final stages of cardiovascular disease. By observing the existence of ischemic myocardial diseases in populations with low incidence of coronary artery atherosclerosis, studies have shown that ischemic heart disease is not only associated with atherosclerosis, but also to vascular aging. This finding led to the publication of O’Rourke’s third manuscript in 2010, which presented an additional model: vascular aging continuum. The evolution of this model allowed focusing on preventive treatments for the risk factors of CAA and the search for therapies capable of preventing endothelial damage caused by vascular aging and modulating oxidative stress. This review aims to bring together the leading studies that support the evolution of the cardiovascular continuum model over 25 years.

Keywords: Primary prevention; Secondary prevention; Coronary artery disease; Atherosclerosis

Introduction

In January 1989, the important workshop “Frontiers in Cardiovascular Therapy and Cardiac Protection — resolved and unresolved issues” was coordinated by professors Victor Dzau and Eugene Braunwald1 (Figure 1), with the participation of major cardiovascular researchers in the clinical, basic and epidemiological fields. This group of scientists evaluated scientific evidence associated with coronary artery atherosclerosis (CAA), the leading cause of death in the United States, and sought to emphasize the importance of early identification of associated factors for the development and progression of CAA. The proposal was a model that associated a sequential chain of etiopathophysiology events involving risk factors and the alterations caused by these factors in the heart and coronary vasculature, resulting in heart failure and progression to death (Figure 2), which in 2006 became known as cardiovascular continuum2,3.
Scientific evidence has shown that this approach strategy using pharmacological measures for different stages of the continuum enabled the reduction of cardiovascular damage and progression to the advanced forms of the disease. Beside this, mortality from cardiovascular disease in the United States declined by about 40%, which shows that the continuum approach may have helped reducing mortality from CAA.

Advances in molecular and cellular biology techniques, discovery of nitric oxide and the study of histopathology of atherosclerotic plaque in human and animal models gradually helped consolidating a view of coronary atherosclerosis as a degenerative immunoinflammatory process, rather than as an inexorable sclerodegenerative process associated with aging of individuals.

At the same time, myocardial ischemic disease has been considered a distinct pathophysiological behavior, particularly in the elderly in Asian countries. There has been significant growth in the prevalence of heart failure with normal ejection fraction (HFNEF). Both conditions are associated with hypertension and aging. These new findings have led Dzau et al. to propose an additional model to cardiovascular continuum — vascular aging continuum, emphasizing the pathobiological processes that lead to aging/hardening of the great arteries and abnormalities of microcirculation.

The purpose of this review is to present the important landmarks of the evolution, over the last 25 years, of the concept of cardiovascular continuum paradigm.

Cardiovascular continuum — Starting point

The workshop “Frontiers in Cardiovascular Therapy and Cardiac Protection: Resolved and Unresolved Issues,” held from January 8 to 10, 1989 in Boston, was led by the physicians Eugene Braunwald and Victor Dzau, involving 37 other North-American participants.

That meeting resulted in the publication of an important document entitled “Resolved and unresolved issues in the prevention and treatment of arterial disease: a workshop consensus statement,” in 1991. The paper was published to summarize and establish what was known and what was still unknown or unresolved on each etiopathophysiology process involved in the final stage of cardiac disease.

Primarily focusing on the risk factors for cardiovascular disease, such as dyslipidemia, hypertension, diabetes, smoking and left ventricular hypertrophy, issues hitherto unresolved for each factor have been clarified.
Risk factors

- Dyslipidemia
  The National Cholesterol Education Program (NCEP) defined serum levels of LDL-cholesterol (low density lipoprotein cholesterol) > 159 mg/dL as a high risk factor for the development of cardiovascular disease and patients with coronary artery disease or two or more risk factors for CAA should reach ≤130 mg/dL levels through lifestyle changes and therapy. At the time, there was no consensus about what would be the best treatment for high levels of triglycerides.

Another issue was the finding that lipoproteins oxidized on the arterial walls were more atherogenic than native LDL-cholesterol, but further methods required to prove that finding. Beside this, they found that HDL-cholesterol (high-density lipoprotein cholesterol) had a protective effect on the development of atherosclerosis.

Medications available to control dyslipidemia represented an addition to intervention diet in patients with high levels, but further information was needed on their long-term effects as well as the effects of combination therapy, such as resins and inhibitors of coenzyme A-hydroxy-3-methyl-glutaryl reductase (HMG CoA reductase) or niacin. These medications were introduced as cholesterol reducers, but although the long-term risk-benefit ratios of reducing cholesterol were unknown, an association was found between families with low levels of LDL and total cholesterol and high longevity.

Over the past 25 years, there has been a great revolution in the understanding of the role of dyslipidemia in the progression of CAA and treatment of this condition. Statins, approved in 1987 by the Food and Drug Administration (FDA), have become the standard therapy in the treatment of hypercholesterolemia and has had its role demonstrated in the regression of atherosclerosis. This effect and the change in composition...
of the plaque be supported by various methods, such as angiographic techniques, magnetic resonance imaging and vascular ultrasound, using statins and synthetic molecules of HDL (HDL milano)\(^8,9\).

- **Hypertension**
The optimal degree of reduction in blood pressure levels for the prevention of CAA, as well as the mechanism of systemic arterial hypertension (SAH) in the genesis and progression of atherosclerosis and in the development of cardiac disease remained unknown\(^1\).

The clinical meaning of metabolic abnormalities associated with antihypertensive drugs, such as dyslipidemia, glucose and electrolytes was still uncertain, whereas these changes could even increase the risk of cardiovascular disease. This fact was questioned as a probable reason for the treatment of mild and moderate hypertension (130-159/85-104 mmHg)\(^10\).

The role of non-pharmacological therapy in the management of hypertension remained undefined and untested. As well as the effects of other second-line antihypertensive drugs, such as diuretics and beta blockers on morbidity and mortality from SAH. Clinical studies demonstrating the potential benefits of antihypertensive treatment in CAA were not conclusive\(^1\).

The treatment of moderate or severe hypertension decreased the progression of hypertensive nephropathy, but the level of reduction of SAH in patients with SAH and kidney disease was not well documented, as well as SAH and diabetes with or without renal failure\(^1\).

Since the 1989 workshop, three classes of antihypertensive drugs had scientific proof due to their efficacy and safety in the management of SAH, and were incorporated as first-line: angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCB), which proved capable of reducing cardiovascular morbidity and mortality in hypertensive patients\(^11\).

From a dietary point of view, salt restriction in foods has become an important measure of SAH prevention among the population, as well as calorie restriction/combat to obesity, with greater emphasis on childhood obesity. Beside this, the dietary approaches to stop hypertension (the DASH diet), based on fresh fruits, vegetables, low-fat dairy, fiber, vitamins and minerals proven to be useful in controlling hypertension\(^12-14\).

- **Diabetes mellitus**
Diabetes mellitus (DM) has been identified as a risk factor for the development of CAA and its presence enhanced other risk factors. The mechanism by which it accelerated the development of CAA was not established, nor the relationship of microalbuminuria with the development of CAA in diabetic patients. The role of the treatment of hypertension and other risk factors in delaying CAA progression in diabetic patients and the identification of the optimal pharmacotherapy for the treatment of hypertension in these patients was not well defined\(^1\).

A new syndrome described by Reaven, the X syndrome (1988) and, subsequently, metabolic syndrome (MS) was then recognized and considered associated with the development of atherosclerosis. In two decades, the role of MS was recognized as a clinical entity of high prevalence in adults and particularly associated with abdominal obesity, risk of infarction and stroke in the studies INTERHEART\(^15\) and INTERSTROKE\(^16\). Abdominal obesity was been studied from the viewpoint of etiophysiology of atherosclerotic diseases of the adipose tissue, which was identified as an important endocrine organ for the production of adipokines capable of promoting cardiovascular inflammation\(^17,18\).

- **Left ventricular hypertrophy (LVH)**
Specific factors that lead to LVH such as genetics, age, intensity and duration of pressure load, the role of pathophysiology of hypertrophy, the differences in the type of hypertrophy and biochemical changes between LVH induced by pressure overload and intense physical activity were not known. The impact of regression of hypertrophy on mortality, on systolic and diastolic functions, arrhythmia, peripheral vascular disease and clinical symptoms was not clear\(^1\).

LVH was recognized as an independent marker of increased cardiovascular mortality and associated factor in the development of systolic (eccentric remodeling) heart failure (HF). Medications that act on the renin-angiotensin-aldosterone system (RAAS), such as ACEI, ARB, mineralocorticoid receptor inhibitors and plasma renin were proven to interfere with the development of myocardial hypertrophy and effect on cardiovascular disease progression\(^19,20\).

Beta-blockers promoted reverse remodeling on the left ventricle and reduction of morbidity and mortality in patients with heart failure with reduced ejection fraction (HFREF)\(^21\).
Myocardial ischemia, plaque rupture and atherothrombosis

The prevalence of myocardial ischemia in the population was not known because there was asymptomatic myocardial ischemia, among other reasons. The reference values on test results to classify patients as CAA patients at high risk and the interrelationship between CAA and sudden death were not yet defined\(^1\).

The mechanisms leading to plaque stabilization, the ultrastructure that constitutes it and its instability factors, besides the different types of atheroma, were not yet well established. Many issues regarding the thrombotic and non-thrombotic mechanisms on the progression of coronary obstruction, the vasoconstriction mechanism associated with thrombus, the formation of mobile thrombus in response to plaque fissure and thrombus in response to ulceration were not clear and there was no specific therapy for prevention\(^1\).

The use of thrombolytic agents had been introduced in cases of acute myocardial infarction (AMI), but the risk-benefit ratio between the period of 6-24 hours post-AMI, its role in cardiogenic shock, and the combined use with antplatelet agents and anticoagulants were not well established. Besides this, there was no scientific basis for the use of myocardial revascularization in acute myocardial infarction, which later became the gold standard method\(^1\).

Myocardial remodeling and the importance of artery patency related to AMI as a determinant in left ventricular dilation was uncertain. In addition, the use of medications such as ACEI in post-AMI and their effectiveness in remodeling were not well defined yet\(^1\).

Nowadays, the use of ACEI, beta-blockers, mineralocorticoid inhibitors in patients with ventricular dysfunction or HF following AMI reduces mortality. Myocardial reperfusion associated with dual-antiplatelet therapy represents the standard therapy currently recommended by the guidelines of Brazilian and international medical societies\(^2^2-2^4\).

Secondary prevention

The role of reducing cholesterol levels in secondary prevention demanded further investigation. Strategies using antplatelet agents, beta-blockers, RAAS inhibitors and statins have progressively become standard medications in secondary prevention\(^1\).

Heart failure

HF is the ultimate expression of the chain of CAA events, consisting of a multisystem syndrome fundamentally associated with cardiac dysfunction, and involves both the heart and the peripheral circulation\(^1\).

Neurohumoral activation is a physiological response to contractile dysfunction. It was believed that this activation also contributed to the pathophysiology of HF, perhaps influencing renal perfusion, sodium excretion, exercise tolerance, ventricular contractility and development of arrhythmias, but the role of stimulation as an independent risk factor was not well understood either. An important issue was whether the beta-adrenergic receptors should be stimulated or blocked in HF\(^1\).

In recent decades, it has been demonstrated, through robust scientific evidence, that beta-blockers, ACEI or ARBs and mineralocorticoid receptor inhibitors reduce morbidity and mortality in HFREF and were then incorporated into the HF treatment guidelines\(^2^5\).

Establishment of cardiovascular continuum and the new era of molecular biology

Important findings about the functions of nitric oxide (NO) in the cardiocirculatory system in the 1980s promoted a change in the scientific community mindset\(^1\).

In 1992, NO was considered the molecule of the year by Science magazine\(^2^6\). In 1998, Ferid Murad, Robert Furchgott and Louis Ignarro (Figure 3) were awarded the Nobel Prize of Physiology and Medicine for discovering the signaling properties of NO.

Endothelial dysfunction and oxidative stress became the basis of CAA understanding. These concepts have influenced this second major publication on cardiovascular continuum, led by Dzau. Studies conducted by the brilliant pathologist Russell Ross et al. have incorporated these sets of information from basic science, supported by the emerging molecular and cellular biology techniques, promoting changes to the clinical practice of etiopathophysiology understanding\(^5\).
Endothelial dysfunction promoted by risk factors such as hypertension, diabetes, smoking and dyslipidemia would lead to functional abnormalities following monocyte infiltration and LDL-cholesterol deposition. This process results in the development of anatomic abnormalities that progressively evolve, forming atherosclerotic plaque (Figure 4). Then, the lymphocyte-modulated immunological phenomena would play a supporting role in the formation and rupture of fibrous plaque, leading to instability and acute events, known as atherotrombosis.5

Dzau’s second manuscript — The Cardiovascular Disease Continuum Validated: Clinical Evidence of Improved Patient Outcomes — published in the journal Circulation in 2006, presents a body of scientific evidence that has been progressively marked in pharmacological interventions at different stages of the cardiovascular continuum, capable of reducing morbidity and mortality.2,3

The role of statins, not only as drugs capable of reducing cholesterol, but also capable of interfering with inflammation has been studied, as well as new agents capable of improving endothelial function and reducing cardiovascular inflammation, such as exercise, antioxidants and vitamins.2,3,5

CAA has a strong inflammatory component. An association between levels of C-reactive ultrasensitive protein (CRP), an inflammatory marker, and CAA risk has been demonstrated. The use of statins reduces CRP
levels indicating an anti-inflammatory effect of the drug on disease progression. Today, new medications with an anti-inflammatory action on CAA have been tested in many clinical trials.\(^7\)

**Vascular aging continuum**

The classical model of the cardiovascular continuum, due to epidemiological changes, advances in etiopathophysiology knowledge and studies on vascular aging, led Dzau to incorporate vascular aging continuum in this model\(^7\) (Figure 5).

The emerging epidemic of HFNEF, a condition associated with hypertension and aging, as well as the emergence of ischemic heart disease in eastern elderly individuals in the absence of obstructive coronary atherosclerosis, point to the need for clinicians and researchers to expand the traditional paradigm of cardiovascular continuum and integrate it to the vascular aging continuum.\(^7\)

This new model described by O’Rourke et al. in 2010 brings an additional insight, emphasizing the vascular aging process, culminating not only in the final stages of CAA, but also in microvascular diseases, mainly affecting richly perfused organs such as the brain and kidneys. This new view is based on the progressive degeneration of the proximal aorta, causing its stiffening and swelling with consequently harmful effects on the heart, brain and kidneys, thus ruling out the idea that CAA would necessarily linked to atherosclerosis.\(^7\)

The vascular aging continuum can be divided into four stages:

- **Stage one**
  Over time, blood flow in the aorta and in the large aged vessels cause micro-lesions of the elastic layer leading to swelling and stiffening of the arterial wall.

- **Stage two**
  It includes the harmful effects of arterial stiffening, increasing left ventricular (LV) workload in combination with reduced coronary perfusion in a way that proximal aorta stiffness would lead to an increased afterload, resulting in increased cardiac work and LHV, generating isolated systolic hypertension. In addition, this increase in LV mass causes perfusion deficit and consequent myocardial ischemia.

---

**Figure 5**
Cardiovascular continuum (left), aging continuum (right) and their interactions.
Source: adapted from O’Rourke et al.\(^7\)
HFREF – heart failure with reduced ejection fraction; HFNEF – heart failure with normal ejection fraction
• Third stage
Arterial stiffening culminates in damping deficit of the arterial pulse wave, transmitted to microcirculation, hence damaging the brain and kidneys. In the brain, these damages are called pulse wave encephalopathy. This aggression harms vascular endothelium by increasing the levels of endothelial cell fragments and C-reactive protein in the circulation, predisposing to thrombosis and infarctions due to inflammation with consequent vascular repair.

• Stage four
It occurs concurrently with stage three and consists in later damage to the heart, which can be explained by coronary perfusion deficit caused by increased muscle mass (LVH) leading to greater need for blood supply that turns out to be insufficient, combined with reduced diastolic period and systolic increase. Both conditions affect the perfusion of coronary ostia, increasing the risk of myocardial ischemia and infarction, even in the absence of significant coronary obstruction.

Both continuum models result in the final stages of CAA. However, as classic risk factors are not directly involved in arterial aging, individuals who do not have significant atherosclerosis can develop myocardial ischemia.

The importance of this additional insight on vascular aging continuum lies in the use of medications that reduce blood pressure, especially central pressure, thereby reducing vascular damage.

Studies using hypertension management drugs should also assess the impact of medications the vascular physiology in hypertensive individuals and in the elderly in order to demonstrate that this new concept may interfere with morbidity and mortality in target organs such as chronic kidney disease, vascular dementia and HF.

Conclusion
Cardiovascular continuum exerts strong influence on the CAA approach by cardiologists and general practitioners from renewed insights on etiopathophysiology through a cascade of pathophysiological events, which allowed the development of evidence-based strategies capable of delaying the progress or improving disease symptoms. Beside this, the concept of cardiovascular inflammation in the context of endothelial dysfunction and atherosclerosis has been gradually established, explaining the effects of risk factors in CAA. A new concept capable of expanding the initial view has been recently proposed by Dzau, associating vascular aging with hypertension in macro and microcirculation, causing myocardial infarction even in the absence of significant vascular obstruction.

Potential Conflicts of Interest
This study has no relevant conflicts of interest.

Sources of Funding
This study had no external funding sources.

Academic Association
This study is associated with the Graduate Program in Cardiovascular Sciences of Universidade Federal Fluminense.

References


