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Review

Coronary microvascular dysfunction and idiopathic dilated cardiomyopathy

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Abstract:
There is growing evidence of the presence and relevance of coronary microvascular abnormalities in many cardiac diseases. In particular, it has been recently shown that dilated cardiomyopathy (DCM) is characterized by dysfunction of the coronary microvessels since its very early onset. Coronary microcirculatory dysfunction is not an effect of myocardial damage but seems in turn to cause progressive contractile impairment, ventricular dilation and heart failure. The mechanisms of the progressive deterioration of cardiac function in DCM are largely unknown but both myocardial hypoperfusion and myocardial ischemia at the microvascular level are most probably involved. It has been demonstrated that the presence and the extent of coronary microcirculatory dysfunction in patients with early stage DCM is an independent and relevant predictor of worse prognosis.
From these studies it is more and more evident that the coronary microcirculation is involved in the pathogenesis of DCM and should be considered a new target of treatment in those cardiac diseases at risk to evolve towards heart failure.

Key words:
dilated cardiomyopathy, coronary microcirculation, ischemia, heart failure

Introduction

Dilated cardiomyopathy (DCM) is a cardiac muscle disease characterized by reduced contractile function and dilation of the left or both ventricular chambers [32].

Idiopathic DCM is frequent and distinct from specific forms of the disease caused by toxic agents (i.e. alcoholic cardiomyopathy), systemic (i.e. diabetic cardiomyopathy) or other cardiovascular disorders (i.e. ischemic cardiomyopathy) [32]. In the present paper we will mainly refer to "idiopathic" DCM.

The incidence of DCM in Europe is 6.95/100,000 new cases a year [30], but this is a rough estimation since there is a growing evidence that the course of the illness is asymptomatic and difficult to recognize for a long period [31]. DCM is a relevant cause of morbidity for arrhythmia and heart failure and it is diagnosed in about half of heart transplant recipients. Though 20% to 45% of new cases demonstrate functional recovery under appropriate treatment, the prognosis remains severe with an average mortality of 20% at 5 years [9].

Because of the epidemiologic and prognostic relevance of DCM, compared to the lack of definite pathogenetic hypothesis, intensive clinical and experimental research is on going to understand the mechanisms of the disease. DCM is also an important clinical model in which to test new treatments targeted to

slow down or reverse the progression from initial myocardial damage to ventricular dysfunction and heart failure.

"Classical" pathogenetic hypothesis in DCM

Classical pathogenetic mechanisms in DCM include genetic etiology, viral etiology and autoimmunity [35].

Genetic factors have a relevant role. In 20% to 50% of patients familiar history of disease can be documented [1, 13]. However, familiar DCM is characterized by a great heterogeneity both in genetic transmission and in phenotype [21]. A single gene mutation, encoding for proteins of the sarcomere or of the cellular skeleton, is the more direct pathogenetic mechanism but is quite rare. Single nucleotide "polymorphisms" in genes encoding for relevant proteins in cardiovascular regulatory systems (β-adrenergic receptors, Renin-Angiotensin system, Endothelin system, etc.) have also been associated with the disease severity, unfourable outcome and response to treatment [5, 8, 14, 26, 28, 29].

Viral etiology and autoimmunity represent alternative pathogenetic mechanisms in DCM. According to a recent hypothesis, the disease may develop in three steps [19]. A virus causes direct myocardial insult, elicites an autoimmune response which in turn promotes progressive myocardial damage, ventricular dilation and heart failure. The hypothesis of an enteroviral infection as an initial pathogenic cause in DCM is supported by studies demonstrating the presence of enteroviral RNA in the myocardial tissue in almost 50% of the examined patients [2] even if, in other series, this figure is highly variable (0–40%) [12, 38].

Other observations stress the importance of the immunological mechanisms. Circulating anti-heart antibodies directed against antigens of potential functional relevance as myocardial myosine [4], β-adrenergic receptors [18] and the ADP-ATP carrier on the mitochondrial membrane [33] have been found in DCM patients. Myocardial infiltrant lymphocytes are also frequent in association with other markers of inflammation. Whether this immunological and inflammatory pattern, independently of the persistence of a viral RNA in the myocardium, may represent the evolution of an acute myocarditis is an open question [34].

DCM and coronary microvascular dysfunction

The pathogenetic mechanisms described above may be considered a leading cause of DCM only in the minority of patients in whom a clear genetic disease or a viral myocarditis can be documented. Besides, even in these patients, the same factors cannot entirely account for progressive cardiac dilation and heart failure. Other mechanisms should be necessarily involved both in the genesis of the disease and in its evolution.

Among these, a potential role for the coronary microvasculature has been recently hypothesized [17]. This hypothesis is consistent with common clinical observation. Cardiomyopathic patients frequently come to medical attention, before the occurrence of overt heart failure, because of chest pain symptoms or ventricular arrhythmias. Regional wall motion abnormalities are often observed and stress perfusion scintigraphy may show resting and stress induced perfusion defects [40]. Similar findings commonly suggest the presence of coronary artery stenosis, which will not be confirmed at cardiac catheterization in these patients, but abonormalities at the coronary microvascular level might similarly be responsible of these observations.

In cardiomyopathies, alterations of the coronary microvascular component may be secondary to the structural and functional alterations of the myocardium. In the presence of severe hypertrophy and/or ventricular dilation and dysfunction different extravascular factors may account for reduced myocardial perfusion at the microvascular level: increase in myocardial mass not adequately vascularized and of ventricular filling pressure as in the hypertrophic cardiomyopathy [6] or increase in wall stress as in advanced DCM with hemodynamic impairment [15]. Moreover, reduced contractile function may imply low energetic demand and consequently a down regulation of myocardial blood flow at rest [39].

More recent studies have shown that the coronary microcirculation may be directly affected in cardiomyopathies. In explanted hearts from patients with end-stage heart failure due to DCM, myocardial blood flow is severely reduced at rest independently of myocardial fibrosis which does not involve more than 20% of the myocardial mass [27]. In hypertrophic cardiomyopathy, as in hypertension, structural altera-

tions of the microvessels, characterized by hypertrophy of the arteriolar wall, can be documented [20]. In DCM similar structural abnormalities have never been demonstrated, but many evidences exist in favour of functional abnormalities of the coronary microvasculature.

Different clinical studies have demonstrated a clear impairment of coronary endothelial function in DCM [36] as part of a systemic alteration of the vascular endothelium [10]. Endothelial dysfunction is able to strongly limit the coronary vasodilatory response to stress. This condition is potentially able to cause an imbalance between myocardial oxygen demand and blood flow delivery setting the "scene" for possible myocardial ischemia.

A relevant question is if endothelial dysfunction arises late in the natural history of the disease, as a consequence of heart failure, or may occur earlier participating to the progression of ventricular dysfunction towards heart failure. An answer to this question comes from the study of patients with early stage disease in whom the effects on the coronary microvessels of hemodynamic impairment and of heart failure induced neurohormonal activation are minimized. Early stage DCM can be recognized by echocardiographic screening in subjects referred to cardiologists because of chest pain, palpitations, ECG abnormalities such as ventricular arrhythmias or conduction defects. The presence of ventricular dysfunction and the exclusion of other cardiac and systemic diseases allow the diagnosis of DCM, once normal vessels have been documented at coronary angiography [22]. The interesting observation is that up to 82% of these patients show reduced myocardial blood flow, at rest and during metabolic and pharmacological vasodilation, due to coronary microcirculatory dysfunction. This finding has been recently obtained by Positron Emission Tomography [23] but had been already reported in advanced disease in the late 60's [16]. Moreover, the severity of flow abnormalities, and hence of microvascular dysfunction, is able to predict the evolution of the disease towards progressive ventricular dysfunction and heart failure [24]. The prognostic relevance of coronary microvascular dysfunction has been confirmed in other cardiovascular diseases such as hypertrophic cardiomyopathy [7] and minimal coronary atherosclerosis [3].

According to these evidences, it is now hypothesized that coronary microvascular dysfunction may have a relevant role in the pathogenesis of heart failure possibly through progressive myocardial ischemic damage. The hypothesis of "microcirculatory" ischemia as a cause of progressive ventricular dysfunction in DCM has been suggested by recent studies. It has been demonstrated that coronary vasodilatory capacity may be both globally and regionally impaired in DCM and that in those regions with severe flow abnormalities, glucose metabolism is increased and aerobic metabolism decreased [25, 37] (Fig. 1). A similar pattern of flow-metabolism "mismatch", reduced myocardial perfusion and enhanced glucose metabolism, in the presence of contractile dysfunction is the distinctive marker of "hibernation" described in patients with coronary artery disease and heart failure

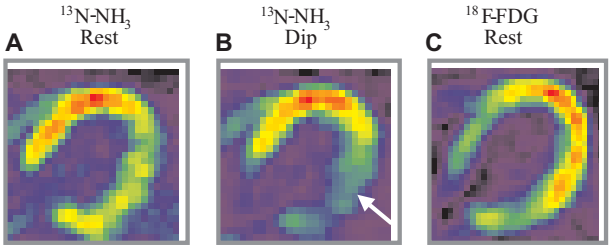

Fig. 1. Scintigraphic images obtained by Positron Emission Tomography in a patient with early stage DCM. The regional myocardial distribution of the flow tracer (13N-Ammoniaca) is shown for a middle ventricular transaxial plane in resting conditions (**A**) and during maximal vasodilation induced by *iv* dipyridamole (**B**). The regional distribution of the metabolic tracer 18F-Fluorodeoxiglucose, injected at rest, is also shown for the same plane (**C**). A perfusion defect involving the posterolateral wall of the left ventricle is present at rest and more evident during dypiridamole (arrow). The same wall shows a relevant increase in glucose metabolism. This flow/metabolism mismatch pattern is suggestive of "microcirculatory" myocardial ischemia

and represents the adaptation of the myocardial tissue to chronic or repetitive ischemia [11]. These similarities between DCM and classical ischemic heart disease strongly suggest that coronary microvascular dysfunction might be able by its own to cause myocardial ischemia and probably contribute to progressive myocardial dysfunction. This fascinating hypothesis, however, awaits for direct confirmative studies.

Clinical implications and conclusions

It is more and more evident that functional and/or structural alterations of the coronary microcirculation can be recognized in many diseases potentially able to

evolve towards progressive ventricular dysfunction and heart failure. These microcirculatory abnormalities are independent of atherosclerotic lesions of the large epicardial arteries or of abnormalities of the myocytic and interstitial component of the myocardial tissue. Altered microvessels are able to limit myocardial perfusion and potentially cause myocardial ischemia. Moreover, they may also release substances that in turn directly affect both the myocardial structure and function.

Accordingly, coronary microvascular dysfunction can be considered one of the pathogenetic mechanisms involved in the evolution of ventricular dysfunction towards heart failure and have an independent and relevant prognostic value even in the absence of coronary artery disease [3, 24]. Hence, the coronary microcirculation is a new therapeutic target in heart failure and in progressive cardiac diseases such as cardiomyopathies.

At present, there are no effective treatment stretegies able not only to antagonize neurohormonal activation and myocardial remodeling but also to improve coronary microvascular function. Such an integrated treatment could be particularly useful in those conditions at risk of progressive ventricular dysfunction and with documented coronary microvascular impairment to prevent the evolution towards heart failure. This field will be surely the matter of intensive research in the next future.

References:

1. Baig MK, Goldman JH, Caforio ALP, Coonar AS, Keeling PJ, McKenna WJ: Familial Dilated Cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol, 1998, 31, 195–201.
2. Bowles NE, Richardson PJ, Olsen EGJ, Archard LC: Detection of Coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet, 1986, 1, 1120–1123.
3. Britten MB, Zeiher AM, Schachinger V: Microvascular dysfunction in mildly diseased or angiographically normal coronary arteries predicts adverse cardiovascular long-term outcome. Coronary Artery Disease, 2004, 15, 259–264.
4. Caforio ALP, Grazzini M, Mann JM, Keeling PJ, Bottazzo GF, McKenna WJ, Schiaffino S: Identification of α and β-cardiac myosin heavy chain isoforms as major autoantigens in dilated cardiomyopathy. Circulation, 1992, 85, 1734–1742.
5. Candy GP, Skudicky D, Mueller UK, Woodiwiss AJ, Sliwa K, Luker F, Esser J, et al.: Association of left ventricular systolic performance and cavity size with angiotensin-converting enzyme genotype in idiopathic dilated cardiomyopathy. Am J Cardiol, 1999, 83, 740–744.
6. Cannon RO, Rosing DR, Maron BJ, Leon MB, Bonow RO, Watson RM, Epstein SE: Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation, 1985, 71, 234–243.
7. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG: Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med, 2003, 349, 1027–1035.
8. Charron P, Tesson F, Poirier O, Nicaud V, Peuchmaurd M, Tiret L, Cambien F et al.: Identification of a genetic risk factor for idiopathic dilated cardiomyopathy. Involvement of a polymorphism in the endothelin receptor type A gene. CARDIGENE group. Eur Heart J, 1999, 20, 1587–1591.
9. Dec GW, Fuster V: Idiopathic Dilated Cardiomyopathy. New Engl J Med, 1994, 331, 1564–1575.
10. Drexler H, Hayoz D, Munzel T, Hornig B, Just H, Brunner HR, Zelis R: Endothelial function in chronic heart failure. Am J Cardiol, 1992, 69, 1596–1601.
11. Dutka DP and Camici PG: Hibernation and congestive heart failure. Heart Failure Rev, 2003, 8, 167–173.
12. Giacca M, Severini GM, Mestroni L, Salvi A, Lardieri G, Falaschi A, Camerini F: Low frequency of detection by nested polymerase chain reaction of enterovirus ribonucleic acid in endomyocardial tissue of patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol, 1994, 24, 1033–1040.
13. Grunig E, Tasman JA, Kucherer H, Franz W, Kubler W, Katus HA: Frequency and phenotypes of familial dilated cardiomyopathy. J Am Coll Cardiol, 1998, 31, 186–194.
14. Herrmann S, Schmidt-Petersen K, Pfeifer J, Perrot A, Bit-Avragim N, Eichhorn C, Dietz R et al.: A polymorphism in the endothelin-A receptor gene predicts survival in patients with idiopathic dilated cardiomyopathy. Eur Heart J, 2001, 22, 1948–1953.
15. Inoue T, Sakai Y, Morooka S, Hayashi T, Takaianagi K, Yamanaka T, Kakoi H et al: Coronary flow reserve in patients with dilated cardiomyopathy. Am Heart J, 1993, 125, 93–98.
16. Klassen GA: Alterations in blood flow and tissue volume of the myocardium of patients with cardiomyopathy. Proceedings of the II Annual Meeting of the International Study Group for Research in Cardiac Metabolism. Milano, Istituto Lombardo – Fondazione Baselli, 1969, 133–139.
17. L'Abbate A, Sambuceti G, Neglia D: Myocardial perfusion and coronary microcirculation: from pathophysiology to clinical application. J Nucl Cardiol, 2002, 9, 328–337.
18. Limas CJ, Limas C: Beta-adrenoceptors antibodies and genetics in dilated cardiomyopathy: an overview and review. Eur Heart J, 1991, 12, Suppl D, 175–177.
19. Liu PP, Mason JW: Advances in the understanding of myocarditis. Circulation, 2001, 104, 1076–1082.
20. Maron BJ, Wolfson JK, Epstein SE, Roberts WC: Intramural ("small vessel") coronary artery disease in hyper-

trophic cardiomyopathy. J Am Coll Cardiol, 1986, 8, 545–557.
21. Mestroni L, Rocco C, Gregori D, Sinagra G, Di Lenarda A, Miocic S, Vatta M et al.: Familial dilated cardiomyopathy:evidence for genetic and phenotipic heterogeneity. J Am Coll Cardiol, 1999, 34, 181–190.
22. Neglia D, Levorato D, Berti S, Marzilli M, Pelosi G, Marcassa C, Bongiorni MG et al.: Diagnosi e caratterizzazione funzionale di iniziale danno miocardico in pazienti con aritmie cardiache. Cardiologia, 1987, 32, 713–719.
23. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, Salvadori P et al.: Myocardial blood flow responce to pacing tachycardia and to dipyradamole infusion in patients with dilated cardiomyopathy without overt heart failure. Circulation, 1995, 92, 796–804.
24. Neglia D, Trivieri MG, Michelassi C, Gallopin M, Pratali L, Poddighe R, Salvadori P et al.: Prognostic value of myocardial blood flow impairment in patients with idiopathic left ventricular dysfunction. Circulation, 2002, 105, 186–193.
25. Neglia D, Sambuceti G, Iozzo P, L'Abbate A, Strauss HW: Myocardial metabolic and receptor imaging in idiopathic dilated cardiomyopathy. Eur J Nucl Med, 2002, 29, 1403–1413.
26. Niu T, Chen X, Xu X: Angiotensin converting enzyme gene insertion/deletion polymorphism and cardiovascular disease: therapeutic implications. Drugs, 2002, 62, 977–993.
27. Parodi O, De Maria R, Oltrona L, Testa R, Sambuceti G, Roghi A, Merli M: Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplation. Circulation, 1993, 88, 509–522.
28. Podlowski S, Wenzel K, Luther HP, Muller J, Bramlage P, Baumann G, Felix SB et al.: Beta1-adrenoceptor gene variations: a role in idiopathic dilated cardiomyopathy? J Mol Med, 2000, 78, 87–93.
29. Port JD, Bristow MR: Altered beta-adrenergic receptor gene regulation and signaling in chronic heart failure. J Mol Cell Cardiol, 2001, 33, 887–905.
30. Rakar S, Sinagra G, Di Lenarda A, Poletti A, Bussani R, Silvestri F, Camerini F: Epidemiology of dilated cardiomyopathy. A prospective post-mortem study of 5252 necropsies. Eur Heart J, 1997, 18, 117–123.
31. Redfield MM, Gersh BJ, Bailey KL, Ballard DJ, Rodeheffer RJ: Natural history of incidentally discovered, asymptomatic idiopathic dilated cardiomyopathy. Am J Cardiol, 1994, 74, 737–739.
32. "Report of the 1995 World Health Organization/International Society and Federation of Cardiology. Task Force on the Definition and Classification of Cardiomyopathies". Circulation, 1996, 93, 841–842.
33. Schultze K, Becker BF, Schulteiss HP: Antibodies to ADP-ATP carrier – an autoantigen in myocarditis and dilated cardiomyopathy – penetrate into myocardial cells and disturb energy metabolism *in vivo*. Circ Res, 1989, 64, 179–192.
34. Schwimmbeck PL, Badorff C, Rohn G, Schulze K, Schultheiss HP: The role of sensitized T-cells in myocarditis and dilated cardiomyopathy. Int J Cardiol, 1996, 54, 117–125.
35. Startari U, Taylor MRG, Sinagra G, Di Lenarda A, Mestroni L: Cardiomiopatia Dilatativa: eziologia, criteri clinici di diagnosi e screening della forma familiare. Ital Heart J, Suppl, 2002, 3, 378–385.
36. Treasure Cb, Vita JA, Cox DA, Fish RD, Gordon JB, Mudge GH, Colucci VS et al.: Endothelium-dependent dilation of the coronary microvascolature is impaired in dilated cardiomyopathy. Circulation, 1990, 81, 772–779.
37. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, Blanksma PK, Siebalink HM, Vaalburg WM, van Gilst WH, et al.: Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol, 2000, 35, 19–28.
38. Weiss LM, Liu XF, Chang KL, Billingham ME: Detection of enteroviral RNA in idiopathic dilated cardiomyopathy and other human cardiac tissues. J Clin Invest, 1992, 90, 156–159.
39. Weiss MB, Ellis K, Sciacca RR, Johnson LL, Schimdt DH, Cannon PJ: Myocardial blood flow in congestive and hypertrophic cardiomyopathy: relationship to peak wall stress and mean velocity of circumferential fiber shortening. Circulation, 1976, 54, 484–493.
40. Yamaguchi S, Tsuiki K, Hayasaka M, Yasui S: Segmental wall motion abnormalities in dilated cardiomyopathy: hemodinamic characteristics and comparison with thallium-201 myocardial scintigraphy. Am Heart J, 1987, 113, 1113–1128.

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