The complex principle of cause and effect

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The association between diabetes and congestive heart failure and its influence on prognosis are widely known and have been extensively documented.^{1–3} Patients with diabetes have more extensive coronary artery disease, lower left ventricular ejection fraction, and congestive heart failure than non-diabetic patients.

Rubler et al first described “diabetic cardiomyopathy” in 1972 based on four adult diabetic patients with congestive heart failure that could not be explained by *coronary artery disease*, hypertension, valvular heart disease, or alcoholism. Subsequently, the term “diabetic cardiomyopathy” as a diastolic and/or systolic heart failure in diabetic patients *in the absence of significant concomitant coronary artery disease* or arterial hypertension has been defined.^{4,5}

Ehl et al documented that diabetes was an independent predictor of a decreased left ventricular systolic function in 2635 patients who underwent myocardial perfusion SPECT. Diabetes was an independent predictor of a decreased ejection fraction besides male sex, presence of typical angina, pharmacologic stress, the summed rest and summed difference score, and thus independent of the presence and extent of coronary artery disease.⁶

On the other hand, our group recently has published data on 400 asymptomatic patients with type 2 diabetes (BARDOT trial). In BARDOT, patients with an abnormal myocardial perfusion SPECT had a significantly lower left ventricular ejection fraction than patients with a normal scan.⁷

Van den Hoogen et al evaluated 525 asymptomatic diabetic patients using the “anatomic approach” (coronary artery calcium and coronary computed tomography angiography). Patients with a normal coronary computed tomography scan had an excellent prognosis (not taking into account any perfusion data). Both the calcium score and the coronary angiography data effectively risk stratified diabetic patients without chest pain.⁸

Von Scholten et al evaluated the functional and structural aspects of atherosclerosis in asymptomatic patients with type 2 diabetes.⁹ These patients who were free of overt cardiovascular disease had a high prevalence of coronary microvascular dysfunction, especially with concomitant albuminuria, suggesting a common microvascular impairment occurring in multiple microvascular beds.⁹ When the calcium score was added to the analysis, there was also a trend ($P = .032$) toward an inverse association with reduced coronary flow reserve (CFR).

In the current issue of the Journal, Juárez-Orozco et al aimed to evaluate the relationship of diabetes and left ventricular ejection fraction when quantitative perfusion was taken into account. Their conclusion was that diabetes significantly influenced PET-measured systolic function in patients without prior myocardial infarction, independently of myocardial perfusion parameters. Gender, age, hypercholesterolemia, hypertension, smoking, diabetes, stress myocardial blood flow, and myocardial perfusion reserve were incorporated into the multivariate analysis. Of note, neither information regarding anti-diabetic therapy, effectiveness of the therapy (e.g., HbA1c), microalbuminuria, other end-organ damage nor information regarding lipid lowering therapy was reported in the manuscript, all potentially important factors when it comes to endothelial dysfunction, coronary flow measurements, and the interrelation of diabetes and coronary artery disease.

The conclusion of the current study is supported by the published data: The overall blood flow during stress correlated independently with the left ventricular ejection fraction besides the diabetic status of the patients.

However, some missing facts limit the information content of the paper:

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1. The authors mention that patients were considered as not having suffered a prior myocardial infarction if there was no fixed perfusion defect on the scan result. It would have been interesting to learn how many of these patients already had suffered a (silent) myocardial infarction and therefore were excluded from the study, since silent myocardial infarctions probably are more common than previously thought. In an analysis by Arenja et al, one of 4 patients with suspected coronary artery disease had experienced a silent myocardial infarction; the extent in average was 10% of the left ventricle, and was more common in diabetic patients.¹⁰
2. Since medication (e.g., statins) may have impact on coronary flow reserve,¹¹ it would have been interesting to incorporate medication use into the analysis.
3. How is it evident that diabetic patients with a decreased left ventricular ejection fraction suffered from “diabetic cardiomyopathy,” since no information regarding *coronary artery disease* status has been provided? In addition, not all available PET data have been incorporated into the analysis. PET in general provides a comprehensive evaluation of the coronary circulation.¹¹ Since no coronary angiography data were available (as mentioned in the limitations section), it would have been very useful and interesting to report on regional flow results and on perfusion defect size and extent at rest and also during stress. If it would have been done so, the interpretation might have been more focused: what was the main impact of diabetes? Where did diabetes potentially play the major role in diminishing left ventricular ejection fraction, rather in the epicardial coronary arteries or in the microcirculation of the heart?

The paper by Juárez-Orozco and colleagues nicely demonstrates the complex principle of cause and effect:

1. Left ventricular ejection fraction per se still is one of the most relevant prognostic variables.
2. Diabetic patients probably have a lower ejection fraction than non-diabetic patients, irrespective of the presence of coronary artery disease and coronary flow measurements.
3. The mechanisms why diabetic patients have a lower left ventricular ejection fraction than non-diabetic patients in the absence of coronary artery disease and endothelial dysfunction are still unclear.
4. In an ideal situation as many as possible potential variables that may have impact on the development of diabetic cardiomyopathy should be evaluated in a study using a multivariate analysis approach.

Disclosure

No conflict of interest to declare.

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