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Dr. Leif Thuesen
University Department of Cardiology
Kommunehospitalet
DK-8000 Aarhus C
Denmark

Response from the authors

Dear Sir,

Thuesen and Sandahl-Christiansen comment that our paper [1] confirms the work of Vered et al. [2], which showed that a lesser increase of the left ventricular ejection fraction in response to dynamic exercise occurred in male diabetic patients in comparison with normal control subjects. However, Vered et al. [2] studied a heterogeneous diabetic population which included patients treated with insulin, oral hypoglycaemic agents or diet alone, whereas our study was designed to establish that these abnormalities occur in a homogenous group of Type 1 (insulin-dependent) diabetic patients. Our results are consistent with previous studies [2, 3], but define the radionuclide abnormalities more precisely in this type of diabetes.

Your correspondents suggest that one of the male subjects who underwent myocardial biopsy had no clinical evidence of nephropathy or retinopathy, and that the stress tests (presumably they mean during radionuclide ventriculography) must therefore have been falsely positive. This individual also had an abnormal exercise electrocardiograph, but had normal coronary arteries on coronary arteriography. His cardiac biopsy revealed arteriolar changes and diffuse interstitial fibrosis, which is compatible with our suggestion that the abnormal cardiac function was related to these histological changes. They also allege that "signs" of other diabetic complications usually accompany clinical evidence of "cardiomyopathy" in diabetic patients. This comment illustrates several misconceptions about this putative complication of diabetes. Firstly, all of the studies which have examined cardiac function using non-invasive methods have studied asymptomatic diabetic patients who had no clinical signs of cardiac disease. Secondly, "specific heart disease of diabetes" should be used, as the term "cardiomyopathy" denotes heart disease of unknown aetiology. Thirdly, Shapiro et al. [4] did not state that abnormalities of cardiac function were accompanied by the presence of nephropathy or retinopathy, as cited by your correspondents. In their study [4] a crude scoring system was devised to assess the presence and severity of diabetic complications. Diabetic nephropathy was subdivided as "mild" or "severe", depending on the degree of proteinuria by Albus-tix-testing. An association was found between the complication score and some, but not all, of the echocardiographic estimates of cardiac function. These workers observed a prolonged isovolumic relaxation time and a prolonged interval from minimal dimension to mitral valve opening in diabetic patients with no evidence of complications.

Many of our normal female control group failed to increase their ejection fraction by less than 5% during dynamic exercise, and Thues-

en and Sandahl-Christiansen suggest that this may have resulted from inadequate (i.e. submaximal) exercise. All of our male and female subjects (both diabetic and non-diabetic) were exercised until exhaustion, and the mean rise of ejection fraction in the female control group was less than in the male control group. We emphasised this sex difference in our paper, and it is now clearly recognised that equivalent changes in ejection fraction of male and female subjects cannot be defined as abnormal [5].

Finally, your correspondents refer to earlier work by Regan et al. [6], in which a group of diabetic patients were studied who had symptoms of cardiac disease but had no evidence of coronary heart disease on invasive testing. During cardiac catheterisation they demonstrated an increased intra-ventricular pressure which was proposed as evidence for a "cardiomyopathic" process. In the same publication post-mortem histological data was presented from other diabetic patients who had died from heart failure, but who had no evidence of coronary heart disease. This showed the presence of changes in the interstitium consistent with a specific heart disease of diabetes. We have combined these functional and histological aspects in the present study by demonstrating abnormal cardiac function in a group of *asymptomatic* diabetic patients, and have shown that histological changes occur in myocardial tissue from the *same* patients. We submit that this approach has provided convincing evidence for the existence of a specific heart disease of diabetes.

Yours sincerely,

B. M. Fisher, H. J. Dargie and B. M. Frier

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Dr. B. Miles Fisher
Greater Glasgow Health Board-West 1
Gartnavel General Hospital
1053 Great Western Road
Glasgow G12 0YN
UK

Left ventricular dysfunction in diabetes: evidence for the impact of metabolic factors

Dear Sir,

It was of great interest to read the paper by Fisher and coworkers [1] on cardiac function and coronary arteriographic and myocardial biopsy findings in asymptomatic Type 1 (insulin-dependent) diabetic

patients. The authors reported that insulin-dependent diabetic patients, in whom left ventricular ejection fraction (EF) as assessed by radionuclide ventriculography was normal at rest, had a poor increase or even a decrease in EF during dynamic exercise. Coronary angiography and endomyocardial biopsy were performed on 8 of the 16 patients with an abnormal EF response to dynamic exercise. All these 8 patients had normal coronary arteries, but biopsy specimens showed arteriolar wall thickening and interstitial fibrosis in 5 patients and basement membrane thickening suggestive of diabetic microangiopathy in 2 patients. It is logical to consider that diabetic microangiopathy involving myocardium may be causally related to the impaired left ventricular function observed in these patients, but, as the authors emphasize, other factors may also be involved. There is both experimental and clinical evidence to suggest that metabolic abnormalities may play a role in this respect. Thus, impaired left ventricular function or diabetic cardiomyopathy in experimental diabetes is corrected with insulin therapy [2, 3]. We reported some years ago an improvement of systolic time intervals (STI) in a group of newly diagnosed Type 2 (non-insulin-dependent) diabetic patients after starting diet therapy for diabetes. The correction in STI was correlated with the decline in fasting blood glucose level. Furthermore, physical working capacity of the diabetic patients improved concomitantly with the correction of STI and hyperglycaemia [4]. The results yielded indirect evidence for reversibility of impaired left ventricular function. Recently, we evaluated left ventricular systolic function at rest and during exercise in 9 Type 2 diabetic patients with low postglucagon C-peptide, indicating partial insulin deficiency. Before starting insulin treatment these patients showed a prolonged pre-ejection period (PEP) and an elevated PEP/LVET-ratio at STI-registration. In addition, the patients had a poor increase in EF during exercise as assessed by radionuclide ventriculography. After starting insulin therapy the metabolic control improved; concomitantly the abnormalities in STI changed to the normal direction, and EF response to dynamic exercise improved significantly (J. Mustonen et al, unpublished results), confirming our previous findings on newly diagnosed Type 2 diabetes. Therefore, we emphasize that metabolic disturbances, e.g. hyperglycaemia, insulin resistance or other related metabolic abnormalities, may play an important role in the pathogenesis of left ventricular dysfunction in patients with Type 2 diabetes. This dysfunction is not necessarily a "long-term" complication of diabetes, since it may be present already at the time of diagnosis of Type 2 diabetes and, as observations show, it may be reversible by improved metabolic control.

Yours sincerely,

M. Uusitupa, J Mustonen, M Laakso and K Pyörälä

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Dr. Matti Uusitupa
Department of Medicine
Kuopio University Central Hospital
70210 Kuopio 21
Finland

More on the question of a specific heart disease in diabetes

Dear Sir,

I was interested to read the recent report by Fisher et al. [1] in which the authors conclude that abnormalities in left ventricular function in diabetic patients with normal coronary angiography are due to underlying specific diabetic heart disease.

The presence of fibrosis and basement membrane thickening in biopsy specimens from hearts of diabetic patients has been previously reported. However, the authors' histological data is based on only 8 patients; only 5 of the patients showed interstitial fibrosis and only 2 showed basement membrane thickening. The authors themselves comment that the latter observation may well be due to artefact. While they have attempted to relate these pathological features to measurements of left ventricular function, this is a very small number of patients on which to base firm conclusions. In addition, their specimens were from the *right* ventricle while they were measuring *left* ventricular function.

It has been shown [2, 3] that left ventricular function may vary over time, depending on diabetic control, and a one-off measurement of left ventricular function need not imply permanent change. The authors have carried out their measurements once only, and cannot conclude that any observed abnormalities of left ventricular function are fixed or permanent. Under these circumstances, it is invalid to relate histological conclusions to functional studies.

In contrast to the authors' conclusions, I would suggest that their evidence is not substantive enough to support the concept of a specific heart disease in diabetes, although this remains a possibility. They may well have added a further piece to the jigsaw which in time, hopefully, will become completed.

Yours sincerely,

A. D. B. Harrower

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Dr. A. D. B. Harrower
Monklands District General Hospital
Medical Unit
Monks Court Avenue
Airdrie ML6 0JS
UK

Prevalence of diabetes mellitus in elderly subjects in east Finland

Dear Sir,

In a recent article by Tuomilehto et al. [1] published in *Diabetologia*, very high prevalence rates for diabetes mellitus in east Finland were reported. According to their results, 30% of men aged 65 to 84 years had diabetes and 32% had impaired glucose tolerance (IGT).