Available online at ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com
Diabetes & Metabolism 35 (2009) 364–370

Original article

Arterial stiffness and the autonomic nervous system during the development of Zucker diabetic fatty rats

E. Cosson [a,b,c,*], P. Valensi [b,c], D. Laude [a,1], D. Mesangeau [d], H. Dabire [a,2]

[a] *Inserm, EMI-U0107, Paris, France*
[b] *Paris-Nord University, Laboratory of Nutrition, Metabolic diseases and Cardiovascular Prevention, Bobigny, France*
[c] *CRNH-IdF, Department of Endocrinology-Diabetology-Nutrition, Jean-Verdier Hospital, AP–HP, avenue du 14-Juillet, 93143 Bondy cedex, France*
[d] *Merck Santé, Chilly-Mazarin, France*

Received 26 November 2008; received in revised form 23 February 2009; accepted 24 February 2009
Available online 3 August 2009

Abstract

Aim. – This study aimed to investigate the role played by sympathovagal balance in arterial stiffness, a common feature of insulin resistance and type 2 diabetes.

Methods. – We investigated the relationship between autonomic nervous system activity and arterial stiffness in Zucker diabetic fatty rats (ZDF: Gmi-*fa/fa*) and their age-matched controls (lean: *?/fa*). Using simultaneous catheterization of the proximal and distal aorta, we measured intra-arterial blood pressure (BP), heart rate (HR), their variability (spectral analysis) and aortic pulse wave velocity (PWV) in a series of at least six conscious rats aged 6, 12, 18 and 24 weeks.

Results. – BP and PWV increased with age ($P < 0.001$) in both strains with no differences between strains, despite the insulin resistance already present at 6 weeks in ZDF rats. HR was significantly lower ($P < 0.001$) in ZDF than in lean rats. In ZDF compared with lean rats, the low-frequency (LF) component of the systolic BP variations and the LF/high-frequency (HF) component of the pulse interval (PI) variation ratio were reduced ($P < 0.01$ and $P < 0.05$, respectively), while the HF component of the PI (HF-PI) variation was raised ($P < 0.05$). PWV was negatively correlated with HF-PI ($r = -0.37$, $P < 0.01$), but not with biochemical parameters. HF-PI was an independent variable explaining the variation in PWV.

Conclusion. – During the development of disease of ZDF rats, sympathovagal balance might account for the lack of increase in PWV.

Keywords: Pulse wave velocity; Conscious rats; Spectral analysis; Intra-arterial blood pressure measurement

Résumé

Rigidité artérielle et système nerveux autonome pendant le développement du rat Zucker Diabetic Fatty.

Objectif. – Explorer le rôle de la balance vagosympathique dans la rigidité artérielle, souvent associée à l'insulinorésistance et au diabète de type 2.

Méthodes. – Nous avons cherché les relations entre le système nerveux autonome et la rigidité artérielle chez des rats Zucker Diabetic Fatty (ZDF : Gmi-*fa/fa*) et leurs témoins (Lean [*?/fa*]) appariés selon l'âge. Nous avons mesuré la pression artérielle (PA), la fréquence cardiaque (FC), leurs variabilités par analyse spectrale et la vélocité de l'onde de pouls fémoro-aortique (VOP) grâce à un cathétérisme simultané de l'aorte proximale et distale chez au moins six rats non anesthésiés âgés de six, 12, 18 et 24 semaines.

* Corresponding author.
E-mail address: emmanuel.cosson@jvr.aphp.fr (E. Cosson).
[1] Current affiliation: Inserm, Unité 872, 75270 Paris, France
[2] Current affiliation: Inserm, Unité 955, 94704 Maisons-Alfort, France.

1262-3636/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.diabet.2009.02.007

Résultats. – La PA et la VOP ont augmenté avec l'âge ($P < 0{,}001$) sans différence entre rats ZDF et Lean malgré une insulinorésistance déjà présente à six semaines chez les rats ZDF. La FC était plus basse ($P < 0{,}001$) chez les rats ZDF que chez les rats Lean. La composante de basse fréquence de la variabilité de la PA systolique et le rapport composante de basse fréquence/composante de haute fréquence de la variabilité de la FC était réduit chez les rats ZDF comparés aux rats Lean ($P < 0{,}01$ et $P < 0{,}05$, respectivement), alors que la composante de haute fréquence des variations de FC (HF-FC) était augmentée ($P < 0{,}05$). La VOP était en corrélation négative avec HF-FC ($r = -0{,}37$, $P < 0{,}01$), mais non avec les paramètres biochimiques. HF-FC était une variable indépendante expliquant la variance de la VOP.

Conclusion. – Lors du développement des rats ZDF, la balance vagosympathique pourrait participer à l'absence d'augmentation de la vélocité de l'onde de pouls.

Mots clés : Vélocité de l'onde de pouls ; Rats conscients ; Analyse spectrale ; Mesure intra-artérielle de la pression artérielle

1. Introduction

Diabetes, obesity, hypertension and dyslipidaemia all contribute to vascular remodeling and, as a consequence, arterial stiffening. Arterial rigidity, determined by an increased pulse pressure or pulse wave velocity (PWV), is a strong and independent predictor of coronary risk in subjects with diabetes, hypertension and chronic renal failure [1,2].

The autonomic nervous system plays a key role in blood pressure (BP) regulation and is also involved in obesity-induced hypertension [3]. Its influence on arterial stiffness was also suggested in the late 1990s [4,5]. In humans, arterial stiffness has been associated with high sympathetic activity in hypertensive patients with [6] and without [7] type 2 diabetes, and in healthy individuals as well [8]. In addition, depressed vagal activity has also been associated with increased arterial stiffness [9]. Previously, we have found an association between sympathetic activity and arterial distensibility in spontaneously hypertensive rats (SHR) [10] and, more recently, a negative correlation between vagal activity and PWV in Wistar–Kyoto (WKY) rats [11]. Furthermore, data obtained in a model of rats with massive obesity have suggested that enhanced vagal activity may protect against hypertension [12]. However, such findings were observed in animal models with hypertension as a unique feature [10], or with major metabolic disorders linked to obesity, but not diabetes [12].

The Zucker diabetic fatty (ZDF) rat is a model of type 2 diabetes and obesity that exhibits a number of predisposing metabolic factors for an increased BP and arterial stiffness such as obesity and dyslipidaemia [13–16]. Nevertheless, conflicting results have been reported regarding BP levels in ZDF rats. These discrepancies might be ascribed to the methods used to record BP, including tail-cuff plethysmography [13–16] and intra-arterial determinations made under anaesthesia [17,18]. As for arterial rigidity, to our knowledge, only one report has described an increased index of arterial stiffness under anaesthesia in ZDF rats aged 10 weeks [18]. Thus, exploring intra-arterial BP and PWV in conscious unrestrained ZDF rats during disease development remains a critical issue.

For this reason, power spectral analysis of heart rate variability (HRV) has been introduced to detect autonomic dysfunction in diabetic patients and can therefore serve as a clinical test of autonomic function [19,20]. Yet, to our knowledge, the autonomic nervous system has remained unexplored in ZDF rats, the report of Towa et al. [19] having been performed in Zucker fatty rats, a model of insulin resistance without diabetes. Indeed, in ZDF rats, changes in the sympathovagal balance related to the different disease stages (obesity and insulin resistance, then diabetes and, finally, weight loss) are expected.

The aims of the present study were:

- to investigate changes in intra-arterial BP and aortic PWV in conscious, freely moving ZDF rats at different times in the development of diabetes from ages 6 to 24 weeks;
- to explore autonomic nervous function with the use of power spectral analysis of BP and heart rate (HR);
- to identify the possible factors that might have an influence on BP and PWV, in particular, the metabolic changes and indices of the autonomic nervous system derived from BP and HR variability.

2. Methods

2.1. Animals

Male ZDF rats (Gmi-*fa/fa*; $n = 30$) and their age-matched male controls (lean *?/fa*; $n = 28$) were obtained from Charles River Laboratories France (L'Arbresle, France) at 5 or 6 weeks of age and acclimatized for at least 1 week before the experiments. The animals were maintained at a temperature of 22–24 °C, with a light on from 06:00 to 18:00 every day, and given access to chow (A04; UAR, France) and tap water ad libitum. The measurements were taken when the animals were 6, 12, 18 and 24 weeks of age. The experimental protocol was approved by the animal ethics committee of the Institut National de la Santé et de la Recherche Médicale (National Institute of Health and Medical Research) in Paris, France. All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, published by the US National Institutes of Health.

2.2. Blood pressure and pulse wave velocity

The technique for measuring PWV in rats has been described in detail elsewhere [11]. Briefly, the rats were anaesthetized with sodium pentobarbital (60 mg/kg intraperitoneally). Two polyethylene catheters – a PE-10 (2 cm in length, inner diameter [ID] 0.28 mm, outer diameter [OD] 0.61 mm; Clay Adams, Parsippany, NJ) connected to a PE-50 (15 cm in length, ID