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Diabetes & Metabolism xxx (2016) xxx–xxx

Original article

Effects of glycaemic variability on cardiac remodelling after reperfused myocardial infarction: Evaluation of streptozotocin-induced diabetic Wistar rats using cardiac magnetic resonance imaging

M. Joubert [a,i,*], J. Hardouin [a,i], D. Legallois [b,i], K. Blanchart [b,i], N. Elie [c], M. Nowoczyn [d,i], P. Croisille [e,f], L. Coulbault [d,i], C. Bor-Angelier [g], S. Allouche [d,i], A. Manrique [h,i]

[a] *Diabetes Care Unit, Caen University Hospital, Caen, France*
[b] *Cardiology Unit, Caen University Hospital, 14033 Caen, France*
[c] *CMABIO-HIQ Facility, SF4206 ICORE, IBFA, University of Caen, 14000 Caen, France*
[d] *Biochemistry Unit, Caen University Hospital, 14000 Caen, France*
[e] *Radiology Department, Saint-Etienne University Hospital, 42000 Saint-Etienne, France*
[f] *CREATIS CNRS UMR5220 Inserm U1044, Lyon University, 69000 Lyon, France*
[g] *Pathology Department, F.-Baclesse Cancer Center, 14000 Caen, France*
[h] *Nuclear Medicine Department, Caen University Hospital, 14033 Caen, France*
[i] *EA4650 Normandie université, GIP Cyceron, 14000 Caen, France*

Received 8 December 2015; received in revised form 27 January 2016; accepted 15 February 2016

Abstract

Aims. – In addition to hyperglycaemia, glycaemic variability seems to be associated with poor outcomes after acute myocardial infarction. This study explored the impact of glycaemic variability in diabetic Wistar rats subjected to myocardial ischaemia/reperfusion.

Methods. – Animals with streptozotocin-induced diabetes received insulin either to maintain stable hyperglycaemia (Dh group) or to generate glycaemic variability (Dv). After experimental myocardial ischaemia/reperfusion was surgically induced, 7T cardiac magnetic resonance imaging (CMR) was performed at weeks 1 (w1) and 3 (w3).

Results. – Twenty-six rats were randomized [sham group (S): $n=5$; control group (C): $n=7$; Dh group: $n=6$; and Dv group: $n=8$]. The mean amplitude of glucose reflecting glycaemic variability was higher in the Dv than in the Dh group (9.1 ± 2.7 mmol/L vs 5.9 ± 1.9 mmol/L; $P<0.05$). CMR assessment at w3 revealed ventricular enlargement in both Dh and Dv groups compared with the C and S groups (end-diastolic volume: 1.60 ± 0.22 and 1.36 ± 0.30 mL/kg compared with 1.11 ± 0.13 and 0.87 ± 0.11 mL/kg, respectively; $P<0.05$). Circumferential strain was altered between w1 and w3 in the remote area only in the Dv group, resulting in a lower value in this group than in the S, C and Dh groups (-0.11 ± 0.01 vs -0.17 ± 0.05, -0.15 ± 0.03 and -0.16 ± 0.03, respectively; $P<0.05$). In addition, at w3, oedema was also higher in the remote area in the Dv than in the C group (18.3 ± 4.9 ms vs 14.5 ± 1.7 ms, respectively; $P<0.05$).

Conclusion. – In the context of experimental myocardial ischaemia/reperfusion, our results suggest that glycaemic variability might have a potentially deleterious impact on myocardial outcomes beyond the classical glucose metrics.

Keywords: Animals; Cardiac magnetic resonance imaging; Diabetes; Glycaemic variability; Myocardial oedema; Myocardial ischaemia/reperfusion

Abbreviations: C, control group; CMR, cardiac magnetic resonance imaging; Dh, diabetes group with permanent hyperglycaemia; Dv, diabetes group with high glycaemic variability; EDV, end-diastolic volume; ESV, end-systolic volume; IP, intraperitoneal; IR, ischaemia/reperfusion; LV, left ventricular; LVEF, left ventricular ejection fraction; MAGE, mean amplitude of glycaemic excursion; MI, myocardial infarction; ROI, region of interest; S, sham group; SC, subcutaneous; STZ, streptozotocin; WMS, wall motion score.

* Corresponding author at: Service endocrinologie-diabétologie, CHU de Caen, 14033 Caen cedex 9, France. Tel.: +33 2 31 06 45 75; fax: +33 2 31 06 48 54.
E-mail addresses: dr.michaeljoubert@gmail.com, joubert-m@chu-caen.fr (M. Joubert), hardouin-j@chu-caen.fr (J. Hardouin), legallois-da@chu-caen.fr (D. Legallois), blanchart-k@chu-caen.fr (K. Blanchart), nicolas.elie@unicaen.fr (N. Elie), nowoczyn-m@chu-caen.fr (M. Nowoczyn), pierre.croisille@creatis.univ-lyon1.fr (P. Croisille), coulbault-l@chu-caen.fr (L. Coulbault), c.bor-angelier@baclesse.fr (C. Bor-Angelier), allouche-s@chu-caen.fr (S. Allouche), manrique@cyceron.fr (A. Manrique).

http://dx.doi.org/10.1016/j.diabet.2016.02.002
1262-3636/

1. Introduction

Diabetes mellitus has reached epidemic proportions worldwide and represents one of the leading causes of cardiovascular disease [1,2]. Diabetes has been associated with cardiac remodelling and poor patient prognosis after reperfusion of acute myocardial infarction (MI) [3,4]. Beyond the classical glucose metrics of mean glycaemia and HbA_{1c} levels, glycaemic variability has recently emerged as an important parameter related to all causes of cardiovascular mortality in adults and elderly patients with diabetes [5,6]. This association has also been described in intensive care units in patients with high glycaemic variability, for which both morbidity and mortality are increased regardless of their average glycaemic levels [7].

Post-infarction remodelling is a complex phenomenon seen in an increasing proportion of patients surviving the initial stages of MI. Predictors of left ventricular (LV) remodelling include infarct size, infarct-related arterial patency, anterior location, LV end-systolic volume (ESV) and microvascular obstruction [8]. Pathways involved in the deleterious effects of glycaemic variability have been explored through in vitro and animal studies, but not in the specific context of MI [9]. In various preclinical models of cardiac disease, cardiac magnetic resonance imaging (CMR) has allowed repeated non-destructive cardiac phenotype characterization, and provided reliable information on tissue characterization and LV function assessment [10–12]. In particular, myocardial wall strain can be measured using tagged CMR, and T2-weighted sequences can identify the oedematous reaction in post-infarction myocardium, a phenomenon that occurs due to abnormal fluid retention in the intra- and/or extracellular compartments of myocardial tissue [13–15].

The aim of our present study was to investigate the relationship between glycaemic variability and cardiac remodelling as assessed by preclinical CMR after experimental ischaemia/reperfusion in rats with streptozotocin-induced diabetes.

2. Material and methods

2.1. Animals

All animal experiments were performed according to European Commission Directive 86/609/EEC, and all of the investigations and procedures were approved by our regional animal ethics committee (CENOMEXA 054, authorization #N/01-06-11/10/06-14). Experiments were performed on 18- to 22-week-old male Wistar rats (Janvier Labs; Le Genest-Saint-Isle, France), which were housed individually in a temperature-controlled room synchronized to a reversed 12-h dark–light cycle (dark: 6AM to 6PM; light: 6PM to 6AM).

The animals were randomized into four groups: control (C); sham surgery (S); diabetes with permanent hyperglycaemia (Dh); and diabetes with high glycaemic variability (Dv). Rats from groups Dh and Dv received 70 mg/kg of intraperitoneal streptozotocin (STZ; Sigma-Aldrich Corporation, St. Louis, MO, USA), while rats from groups C and S received vehicle only. Insulin treatment was introduced 48 h after STZ injection. Glargine (Sanofi, Paris, France) at 5 IU/kg/day was injected subcutaneously (SC) at 9AM in group Dh animals, and 15 IU/kg/day were injected SC at 9AM in group Dv animals. Thereafter, the insulin dose was titrated according to a five-point (9AM, 11AM, 2PM, 5PM, 8PM) blood glucose monitoring system (FreeStyle Lite, Abbott Diabetes Care, Witney, Oxfordshire, UK) to maintain hyperglycaemia levels at > 13.75 mmol/L in the Dh group, and to generate daily glycaemic swings of < 8.25 mmol/L but > 13.75 mmol/L in the Dv group.

When insulin titration was completed, blood glucose was monitored weekly until the end of the study using a two-point (9AM, 5PM) blood glucose profile, as the highest and lowest glucose values of the day were generally observed at those two time points, respectively. Randomization, treatments and important time points of the study protocol are summarized in Fig. 1. All animals received standard rat chow (rationed to 30 granules/kg/day) supplied in four meals: 30% of the total dose at 9AM; 20% at noon; 20% at 3PM; and 30% at 5PM. Water was available ad libitum.

2.2. Glucose variability assessment

The mean daily amplitude of plasma glucose between 9AM and 5PM was chosen to assess same-day variability. This parameter was analysed for the whole study period—for weeks 0–4 (before surgery) and weeks 4–7 (after surgery). Between-day variability was evaluated by the standard deviation (SD) of plasma glucose values at 9AM and 5PM.

2.3. Surgery

Four weeks after STZ injection, rats in groups C, Dh and Dv were subjected to a surgical ischaemia/reperfusion (IR) procedure. On the day of surgery, insulin was not administered to diabetic animals to avoid hypoglycaemia. After a short induction using isoflurane 5%, the rats were anaesthetized by intraperitoneal injection of ketamine 100 mg/kg (Panpharma SA, Luitré, France) and xylazine 10 mg/kg (Bayer AG, Leverkusen, Germany). After endotracheal intubation, mechanical volume-controlled ventilation was performed using a rodent ventilator (SAR-830/P Ventilator, CWE Inc., Mount Holly, NJ, USA) and room air (tidal volume: 1 mL/100 g; respiratory rate: 90/min; inspiratory time: 50%). Body temperature was maintained within the physiological range using a heating pad (ATC1000 DC Temperature Controller, World Precision Instruments, Inc., Sarasota, FL, USA). Atelectasis was prevented by maintaining a positive end-expiratory pressure of 15–20 mmHg.

A left thoracotomy was performed at the fourth intercostal space and the pericardium was opened. A 6-0 polypropylene snare ligature was passed around the left descending coronary artery, always at the same level (median third part), to obtain a similar infarct size in all the animals. Confirmation that left coronary occlusion had been achieved was provided by visual observation of regional cyanosis of the myocardial surface and loss of contraction. Perfusion was restored after 30 min of ischaemia by releasing the snare. In the sham-operated animals (group S), coronary artery ligation was not performed.

Please cite this article in press as: Joubert M, et al. Effects of glycaemic variability on cardiac remodelling after reperfused myocardial infarction: Evaluation of streptozotocin-induced diabetic Wistar rats using cardiac magnetic resonance imaging. Diabetes Metab (2016), http://dx.doi.org/10.1016/j.diabet.2016.02.002