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Quantification of GLUT4 Gene Expression in Human Atrial Myocardium of Hypertensive Patients and the Effect of Experimental Ischaemia Thereupon

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Introduction: Transmembrane glucose transport and thus cellular high-energy metabolism of the cardiovascular system depend largely on the insulin-responsive GLUT4 isoform of the trans-membrane glucose transport molecule. GLUT4 plays a key role in the development of myocardial and vascular stiffness, in the context of osmolarity, compartmental water distribution and homeostasis. In hypertensive rats, expression of GLUT4 mRNA as well as the amount of protein in the membrane was found to be decreased. In the context of hypertension and ischaemia, no reports can be found on GLUT4 in human myocardium. Myocardial ischaemia increases glucose uptake through translocation of GLUT1 and GLUT4 from an intracellular compartment to sarcolemma. This appears to be a beneficial effect during ischaemia and possibly recovery. Insulin and ischaemia have additive effects in the increase of in vivo glucose utilisation and augment glucose transporter translocation. Delivery of glucose to the glycolytic pathway appears to be a major controlling site of glycolysis in low-flow ischaemia. While many experimental studies suggest that an increase in glucose uptake and metabolism by the ischaemic myocardium help protect myocardial cells from irreversible injury, little or nothing is known in this context about human cardiac trans-membrane glucose transport, SLC2A4-expression and its regulation. **Methods:** We investigated tissue samples (60–150 mg) from the right atrial auricle from patients with arterial hypertension subjected to cardiac surgery, which were snap-frozen in liquid nitrogen and stored at -70°C until homogenisation. RNA-Isolation and cDNA transcription: Total RNA was extracted by the TRIZOL[®] method (Invitrogen Corp., Carlsbad, CA, USA) and further purified using RNeasy Mini Kit (QIAGEN Inc., Hilden, GER). RNA was transcribed into DIG-labelled cDNA. For reverse transcription of isolated RNA we used the High Capacity cDNA Archive Kit (Applied Biosystems) and the Thermocycler MyCycler[™] from Biorad. Real-time PCR was performed using the LightCycler[®] 2.0 System (Roche). Furthermore, in human cardiac tissue (right auricle), using microarray technique, we first looked at general changes in expression profiles during simulated myocardial ischaemia and then at the behaviour of SLC2A4 (GLUT4, solute carrier family 2 [facilitated glucose transporter], member 4) as well as its regulator gene SLC2A4RG. Then, using real-time PCR (Light Cycler), we quantified GLUT4 mRNA expression changes under ischaemic and control conditions in normotensive and hypertensive patients. **Results:** We showed in 28 patients that GLUT4 mRNA was significantly less expressed in patients with arterial hypertension compared to controls. Using the microarray technique, we found that both the expression of GLUT4 gene (SLC2A4) and its regulator gene remain practically unchanged in experimental ischaemia. In real-time PCR (Light Cycler), the mean ratio for GLUT4 gene expression compared to the housekeeping gene G6PDH was under well oxygenated conditions -0.0052 ± 0.0203 and under N2-simulated ischaemia 0.0179 ± 0.0196 ($n = 8$; $\pm$ SEM). No statistically significant difference could be found between the two groups, however, results show a trend towards a slight increase in expression. **Summary:** Our experiments show that GLUT4 mRNA expression is in fact decreased in arterial hypertension compared to normal controls. From these data, one can deduce that arterial hypertension is genuinely associated with decreased GLUT4 expression. However, no significant changes are seen in the expression of the GLUT4 gene as well as in its regulatory gene after 30 minutes of N2-mediated experimental ischaemia. Similarly, biological processes involved in glucose metabolism are not significantly de-regulated, as are others. This, as well as a slight trend towards up-regulation, can be interpreted as an attempt of the myocyte to maintain the energy metabolism stable under hypoxic conditions. **J Clin Basic Cardiol 2007; 10 (online): 1–6.**

Key words: GLUT4, hypertension, ischaemia, heart

The transport of glucose across cell membranes occurs by facilitated diffusion. Several cDNAs encoding structurally related proteins with the properties of facilitative glucose transporters have been isolated and characterized (GLUT). These molecules regulate trans-membrane glucose transport in various tissues. GLUT4 appears to be of special interest for several reasons, in particular because it is the only GLUT directly regulated/stimulated by insulin. It is found in various tissues such as cardiac and skeletal muscles as well as in adipose tissue [1]. The isolation and characterisation of a monoclonal antibody that specifically recognises this “muscle-fat isoform” GLUT4 revealed that it is a unique isoform, different from the glucose transporters present in erythrocytes, brain, kidney, jejunum and liver. It shows between 50 and 70 % cDNA identity with GLUT1–3. Insulin causes a rapid

and reversible increase in glucose transport activity via GLUT4 in cardiac and skeletal muscle [2].

The interrelation between disturbances in glucose metabolism, hypertension and myocardial ischaemic disease has been known for a long time and thus has been the subject of investigation in a multitude of trials, publications and experimental studies [3–12]. Insulin resistance and reactive hyperinsulinaemia occur not only with obesity, impaired glucose tolerance or non-insulin-dependent (type 2) diabetes mellitus, but also in many non-obese [13], non-diabetic patients with essential hypertension and seem to be largely responsible for the development of hypertension. In the pathogenesis of hypertension, inappropriate vasoconstriction, structural changes of the cardiovascular system [14–16], but also unfavourable distribution of liquid between the compartments,

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play a key role. While the complete cascade of interactions between glucose-metabolism and hypertension has not as yet been completely elucidated, trans-membrane glucose transport is certainly crucial in this setting [1, 2, 17–23]. Despite the scant experimental direct evidence, Ikegami et al postulated the GLUT4 gene as one of the target genes in essential hypertension when accompanied with insulin resistance [24]. In the present project, we wish to intensify our investigational efforts focused on the unknown role played by GLUT4 in the development of hypertension using human atrial tissue and more sophisticated and complex techniques. Glucose and high-energy metabolism play a pivotal role in the development of numerous salient characteristics of myocardial ischaemia, such as the gating properties of specific ion channels, intracellular ion homeostasis, electrical phenomena, contractility and other phenomena [24–27]. Myocardial ischaemia increases glucose uptake through translocation of GLUT1 and GLUT4 from an intracellular compartment to sarcolemma. This appears to be a beneficial effect during ischaemia and possibly recovery. Insulin and ischaemia have additive effects to increase in vivo glucose utilisation and augment glucose transporter translocation. Delivery of glucose to the glycolytic pathway appears to be a major controlling site of glycolysis in low-flow ischaemia. While many experimental studies suggest that an increase in glucose uptake and metabolism by the ischaemic myocardium helps protect myocardial cells from irreversible injury, little or nothing is known in this context about human cardiac trans-membrane glucose transport, GLUT4-expression and its regulation.

Here, we shall investigate in human cardiac tissue, sampled from the right auricle, to which extent GLUT4 gene expression is altered in hypertensive patients. We wish to answer the question of whether or not GLUT4 expression is indeed decreased, increased or unchanged in hypertensive patients who are not diabetic and do not show insulin resistance. We also look at the effects of experimental ischaemia/hypoxia on GLUT4 expression in the cardiac tissue of hypertensive and normotensive patients. We hypothesise that down-regulated GLUT4 may be (1) involved in the development of hypertension and (2) lead to less effective protection against myocardial injury. The present study shall be the first step in order to elucidate this interrelation.

Methods

Myocardial tissue samples derived from the right auricle of patients undergoing cardiac surgery. Patients gave informed consent to participate and the project was approved by the local ethics committee of the university. A small part of the right auricle was removed when the heart was put on extracorporeal circulation; this tissue is normally wasted. The sample was then placed in cooled Tyrode solution and transported to the laboratory where it was placed into the experimental chamber as has been done in earlier experiments [16, 26, 28]. The preparation was oxygenated or exposed to 100 % nitrogen and then snap-frozen. Experimental myocardial ischaemia (hypoxia) was simulated by switching 100 % oxygen to 100 % nitrogen (hypoxia) in the perfusate [26]. Then, real-time GLUT4 PCR (Light Cycler 2.0) was used, based on the works of Razeghi et al and Depre et al [29, 30]. Technical details are shown elsewhere [31]. The combined technique of working on a living human preparation in an experimental chamber and the application of RT-PCR with a Light Cycler has been well-established in our laboratory of experimental cardiology over a period of several years in order to be able to answer the particular question of the interactions of hypertension, ischaemia and GLUT4 expression in the human

heart.

Material: Auricula dexter cordis, $\approx$ 100–300 mg; tissue homogenisation was performed using a kryostatic assembly, 50–120 mg of tissue were used for RNA isolation in each experiment.

Solutions: The preparations were continuously superfused with Tyrode solution containing in mM: NaCl 140, KCl 4.5, CaCl₂ 2.5, MgCl₂ 1.0, glucose 10, HEPES 20. Solutions were adjusted to a pH of 7.4 by titration with 4 M NaOH and equilibrated with 100 % O₂/100 % N₂ at 37 °C.

mRNA isolation: Performed with TRIZOL[®] reagent, SmartSpec[™] Plus Spectrophotometer from BIORAD was used in order to assess quantity (260 nm) and quality (ratio 260/280) of mRNA. For reverse transcriptase we used a Thermocycler from BIORAD and further used the High Capacity cDNA Archive Kit from Applied Biosystems.

Quantitative mRNA measurements: we used LightCycler 2.0 (Roche) and as a housekeeping gene glucose 6 phosphate dehydrogenase – Hybridization probes format; our target gene was GLUT4 (SLC2A4) for which we used the TaqMan probe format.

Primer Sequence [29–32]

Forward

5'- GCTACCTCTACATCATCCAGAATCTC – 3'

Reverse

5'- CCAGAAACATCGGCCCA – 3'

TaqMan

5'- FAM – CTGCCAGAAAGAGTCTGAAGCGCCT – TAMRA – 3'

Results

Real-Time PCR

For reverse transcription of isolated RNA, we used the high-capacity cDNA Archive Kit (Applied Biosystems) and the Thermocycler MyCycler[™] from BIORAD. Real-time PCR was performed using the LightCycler[®] 2.0 System (Roche). Figure 1 shows a typical record from our serial real-time PCR measurements. One can see the different numbers of cycles needed for light emission. One can also spot the negative controls.

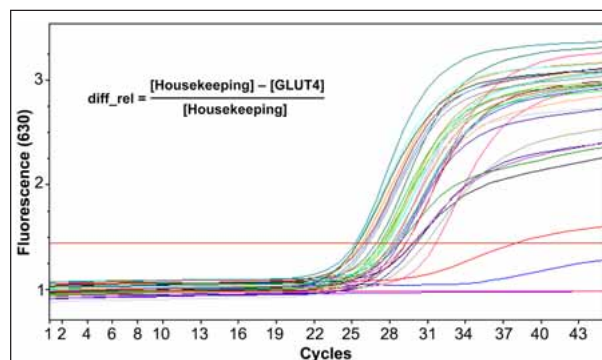


Figure 1. The amount of cycles needed for the amplification curve to exceed the background fluorescence (dashed line) represents the CT value. The quantity of myocardial cellular GLUT4 gene expression is shown as relative difference, which is calculated from the CT values of the housekeeping and the GLUT4 PCR.

Hypertension

GLUT4 expression in hypertensive patients: we showed in 28 patients that GLUT4 mRNA is significantly less expressed in patients with arterial hypertension compared to controls (Tab. 1).

Our results indicate that, in hypertensive patients, GLUT4 expression is reduced in the myocardial tissue. It is noteworthy that reduction of GLUT4 expression is significantly more reduced in patients with severe hypertension than in those with mild hypertension. Interestingly, reduced GLUT4 expression occurred in the right auricle, which is not subject to mechanical stress in hypertension. This suggests that reduced GLUT4 expression is not a phenomenon secondary to mechanical stress alone, but an independent phenomenon, possibly crucial in the natural history of hypertension.

Ischaemia in Control Subjects

General effects of simulated ischaemia upon GLUT4 and its regulator gene: using the microarray technique, we found that both the expression of the GLUT4 gene (SLC2A4) and its regulator gene remain practically unchanged in experimental ischaemia (Tab. 2).

Validation using real-time PCR (Light Cycler) shows that the mean ratio for GLUT4 gene expression compared to the housekeeping gene G6PDH was under well-oxygenated conditions -0.005 ± 0.020 and under N₂-simulated ischaemia 0.018 ± 0.019 ($n = 8$; $\pm$ SEM; Fig. 2). No statistically significant difference could be found between the two groups, however, results show a trend towards a slight increase in expression. In summary, one can see no difference in the expression of GLUT4 and its regulator gene between hypoxic (100 % N₂) and non-hypoxic (100 % O₂) preparations. This could be interpreted as an attempt of the myocyte to maintain a stable energy metabolism under hypoxic conditions.

Ischaemia in Hypertension

Effects of simulated ischaemia/hypoxia upon myocardial GLUT4 expression in hypertensives: interestingly, we found no difference in GLUT4 expression when comparing hypertensive patients with normal controls under ischaemic/hypoxic and normoxic conditions. Noteworthy, after equilibration with 100 % O₂, no differences in GLUT4 mRNA expression were seen between controls and hypertensives (Fig. 3). This is different in tissue samples directly snap-frozen during cardiac surgery, as described in the results section

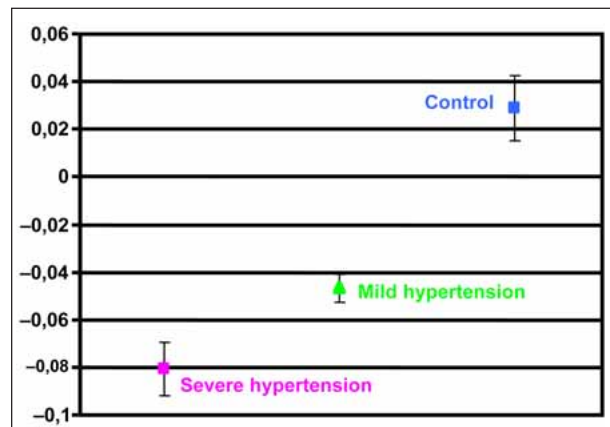


Figure 2. Mean $\pm$ SEM of the relative myocardial cellular GLUT4 gene expression in the three tested groups displays clearly the lower GLUT4 expression in hypertensive patients directly snap-frozen during cardiac surgery, not equilibrated with 100 % O₂.

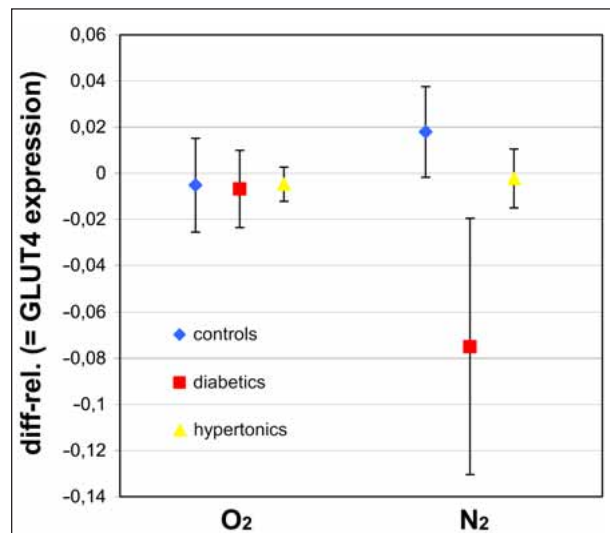


Figure 3. Relative difference in the expression of GLUT4 under ischaemic and non-ischaemic conditions ($n = 8$; $\pm$ SEM) in hypertensive, diabetic and control subjects. Results show slight trends in GLUT4 mRNA expression, however no statistical significance could be seen in either group.

Table 1. GLUT4 expression in hypertensive patients

	Severe hypertension	Mild hypertension	Controls
n	10	10	8
Mean	-0.0806713	-0.04671381	0.02892228
SEM	0.01127767	0.00573899	0.01373076

Table 2. Microarray-results for the expression of GLUT4 gene (SLC2A4) and its regulator gene (SLC2A4RG). Ratio of the normalized signal under well-oxygenated and ischaemia conditions.

Gene ID	Gene symbol	Gene name	Normalized signal O	Normalized signal N	Ratio O/N	log2 ratio O/N
hCG42005.3	SLC2A4	solute carrier family 2 (facilitated glucose transporter), member 4	3.77	4.03	0.94	-0.10
hCG22760.2	SLC2A4RG	SLC2A4 regulator	7.06	6.97	1.01	0.02

(“hypertension”). Hypertensives as well as controls do not change GLUT4 expression after 30 minutes of N₂-simulated ischaemia/hypoxia when initially equilibrated with 100 % O₂, as can be seen in Figure 3. This also argues for stable transmembrane energy supply during conditions of ischaemia both in hypertensives and normotensives. However, diabetic non-hypertensive patients show a trend to reduce GLUT4 expression during ischaemic conditions. This could partially account for the differential response to ischaemia of diabetic subjects.

Discussion

Firstly, we shall discuss the quality of our experimental approach: quality as well as quantity of isolated mRNA were double-checked using both spec-

trophotometry as well as the Agilent's Bioanalyzer 2100 system. Real-time PCR was performed according to the two-step method using Taq polymerase and led to ideal exponential amplification curves as can be seen in Figure 1. Negative controls showed no activity or contamination. Real-time PCR (Light Cycler) is a well-established method in the core facility "Molecular Biology" (CF-MB) of our university and is operated and supervised by an experienced team. The AB1700 microarray system available at the CF-MB is operated by a team consisting of four members with many years of experience in various microarray techniques and platforms (Affymetrix, cDNA and oligonucleotide arrays). To evaluate the performance of the novel Applied Biosystems microarray technology a multicenter proof-of-principle study was conducted by the CF-MB, which included Affymetrix, cDNA- and oligonucleotide-based platforms and that was performed at approved international facilities. The novel AB1700 chemiluminescence microarray system turned out to be excellent with respect to sensitivity and reliability. The results of our experiments have been reproducible and experiments were conducted in accordance with international standards.

Are there solid arguments for an involvement of the insulin-dependent trans-membrane glucose transport molecule in the natural history of hypertension? The following factors affect GLUT4 expression: while different types of muscle fibres contain different levels of GLUT 4 proteins and gene expression as well as different insulin sensitivities, the nutritional state and contractile activity appear to regulate GLUT4 gene expression. Fasting, for example, results in a two- to threefold increase in GLUT4 protein and gene expression in mixed soleus and gastrocnemius muscle preparations [17]. Exercise also increases GLUT4 protein levels in rat skeletal muscle [18], whereas there are conflicting results concerning patients with NIDDM: In skeletal muscle, Handberg et al found no significant difference in the levels of GLUT4 mRNA and protein in biopsies from patients with and without NIDDM [19], whereas Dohm et al found a significantly decreased expression of GLUT4 in the skeletal muscle of insulin-resistant patients [20]. Eckel and Reinauer showed that GLUT4 mRNA is decreased in rat cardiac tissue of streptozotocin-diabetic rats [21]. Interestingly, in the human heart, our own group showed that, in NIDDM patients, GLUT4 mRNA expression is down-regulated [22], whereas it is up-regulated in IDDM [23]. The latter may be explained by the fact that the application of insulin stimulates the expression of GLUT4 mRNA [1].

The multitude of humoral, structural, genetic and molecular mechanisms involved in the pathophysiology of hypertension and its development shall not be completely revealed in this context, but has been subject of research and speculation for more than two centuries, beginning with the work of Stephen Hales and the revolutionary publication of Riva-Rocci [3–7]. The interrelation between disturbances in glucose metabolism, hypertension and myocardial ischaemic disease has been known for a long time and thus it has been the subject of investigation in a multitude of trials, publications and experimental studies [3–12]. Insulin resistance and reactive hyperinsulinaemia occur not only with obesity, impaired glucose tolerance or non-insulin-dependent (type 2) diabetes mellitus, but also in many non-obese [13], non-diabetic patients with essential hypertension and seem to be largely responsible for the development of hypertension. The common coexistence of genetic predisposition for hypertension with insulin resistance helps explain the frequent, although temporally often dissociated, occurrence of hypertension together with dyslipidaemia, obesity and type 2 diabetes in a given cohort. In the pathogenesis of hypertension,

inappropriate vasoconstriction, structural changes of the cardiovascular system [14–16], but also unfavourable distribution of liquid between the compartments play a key role. While the complete cascade of interactions between glucose metabolism and hypertension has not been elucidated completely as yet, trans-membrane glucose transport is certainly crucial in this setting [1, 2, 17–23].

GLUT4, the insulin-dependent trans-membrane glucose-facilitative transport molecule, plays a decisive role in insulin-dependent cardiac glucose metabolism, apparently also for myocardial [33] and vascular stiffness [12] as well as in the context of osmolarity, compartmental water distribution and homeostasis [1]. As early as 1995, comparative studies using nuclear magnetic spectroscopy in the heart of normotensive (WKY) and spontaneously hypertensive rats (SRH) looked at glucose uptake during insulin stimulation as well as at mRNA expression of GLUT1 and GLUT4 [34]: in hypertensive rats, expression of GLUT4 mRNA as well as the amount of protein in the membrane was decreased and cardiac hypertrophy increased by 59 %. Similar results were found in the afferent vessel of the renal glomeruli in experimental, streptozotocin-induced diabetes mellitus. In diabetic animals, GLUT4 as well as polypeptide expression and thus glucose uptake were reduced. In this context, it has been speculated that the resulting decrease of GLUT4 could modulate renal blood flow and, in turn, lead to hypertension.

We then concluded that defective GLUT4 expression may also occur in human myocardium of diabetics [3, 22, 23] as well as hypertensives, and were the first to demonstrate a decreased GLUT4 expression in the right auricle myocardium of non-diabetic hypertensive patients, however, using semi-quantitative techniques and a small cohort of patients [35] (snap-frozen, non-ischaemic human material was difficult to retrieve). Disturbed trans-membrane glucose transport may also significantly contribute to the development of severe coronary heart disease [36] and diabetic cardiomyopathy [37]. In the context of hypertension, very few authors have looked at evidence for myocardial and vascular GLUT4 involvement in the development of hypertension in animals [38] and still no reports can be found on GLUT4 in human myocardium. Despite the scant experimental direct evidence, already Ikegami et al postulated the GLUT4 gene as one of the target genes in essential hypertension when accompanied by insulin resistance [24]. In the present project, we intensified our investigational efforts focussed on the unknown role played by GLUT4 in the development of hypertension using more sophisticated and complex techniques.

In this study, we showed that, in hypertensive patients, GLUT4 expression is reduced in myocardial tissue. It is noteworthy that reduction of GLUT4 expression was significantly more reduced in patients with severe hypertension than in those with mild hypertension. Interestingly, reduced GLUT4 expression occurred in the right auricle, which is not subject to mechanical stress in hypertension. This suggests that reduced GLUT4 expression is not a phenomenon secondary to mechanical stress alone, but an independent phenomenon, possibly crucial in the natural history of hypertension.

GLUT4 and Myocardial Ischaemia

Glucose and high-energy metabolism play a pivotal role in the development of numerous salient characteristics of myocardial ischaemia, such as the gating properties of specific ion channels, intracellular ion homeostasis, electrical phenomena, contractility and other phenomena [25–27]. Many of these aspects of myocardial ischaemia are linked in one way or the other to trans-membrane glucose transport, intracellu-

lar glucose metabolism and, in fact, to GLUT4 [39–41]. Myocardial ischaemia increases glucose uptake through translocation of GLUT1 and GLUT4 from an intracellular compartment to sarcolemma. This appears to be a beneficial effect during ischaemia and possibly recovery. Insulin and ischaemia have additive effects to increase in vivo glucose utilisation and augment glucose transporter translocation [42]. Delivery of glucose to the glycolytic pathway appears to be a major controlling site of glycolysis in low-flow ischaemia. Downstream regulation is then distributed along the pathway with no one site exerting greater inhibition than reduced glucose delivery [43–49]. While many experimental studies suggest that an increase in glucose uptake and metabolism by the ischaemic myocardium helps protect myocardial cells from irreversible injury [45], little or nothing is known in this context about human cardiac trans-membrane glucose transport, GLUT4 expression and the interrelation between the latter and hypertension during ischaemia.

In our experiments on normotensive, non-diabetic control subjects, we can see no difference in the expression of GLUT4 and its regulator gene between hypoxic (100 % N₂) and non-hypoxic (100 % O₂) preparations. This can be interpreted as an attempt of the myocyte to maintain a stable energy metabolism under hypoxic conditions. Hypertensives also do not change GLUT4 expression after 30 minutes of N₂-simulated ischaemia/hypoxia when initially equilibrated with 100 % O₂, as can be seen in Figure 3. This also argues for a stable trans-membrane energy supply during conditions of ischaemia both in hypertensives and normotensives. However, diabetic non-hypertensive patients show a trend to reduce GLUT4 expression in ischaemic conditions. This could partially account for the differential response to ischaemia of diabetic subjects.

In summary, myocardial GLUT4 mRNA expression is reduced in hypertension, possibly indicating a crucial role of this molecule in the development of hypertension. Furthermore, our experiments show that GLUT4 expression remains unaffected by ischaemia/hypoxia. This can be interpreted as an attempt of the myocyte to maintain energy metabolism stable under hypoxic conditions.

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