Relation with Preoperative Fructosamine and Autonomic Nerve Function and Blood Pressure during Anesthesia in Diabetics: A Retrospective Study

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GOTO, Y., SUGIURA, Y., YANAGIMOTO, M., YASUDA, Y., SUZUKI, H. and HASEGAWA, K. Relation with Preoperative Fructosamine and Autonomic Nerve Function and Blood Pressure during Anesthesia in Diabetics: A Retrospective Study. Tohoku J. Exp. Med., 1999, 187 (1), 49–58 — Many diabetics may have a high risk involving the cardiovascular system. In an attempt to predict the intraoperative risks of diabetics during anesthesia, we evaluated retrospectively the relationship among the biochemical assay or autonomic nerve function obtained as parts of the preoperative examination, and the blood pressure changes relating to the stimulation of intubation and extubation for anesthesia. In 40 diabetic surgical patients examined the biochemical assay (HbA1c, fructosamine level and blood glucose level) beforehand, the autonomic nerve function was quantified preoperatively by analysis of ECG R-R variability recorded in supine and subsequent standing position using an HRV analyzer, and some parameters of autonomic nerve function especially responsive sympathetic nerve activities were obtained. We assessed the correlation with systolic blood pressure changes in these cases at intubation for general anesthesia comparing to similar conditioned 40 non-diabetics. A diabetics with low vagal activity became larger systolic blood pressure afterdrop at tracheal intubation for anesthesia \((r=0.513, p<0.001)\). Otherwise the blood pressure afterdrop at extubation became larger in a non-diabetics with high sympathetic activity \((r=0.502, p<0.001)\). The preoperative fructosamine concentration in diabetics correlated positively with the responsive sympathetic nerve irritability index; “mRR\((sup)\)-RRmin\((std)\)” \((r=0.432, p<0.05)\) and the responsive sympathetic nerve excitability index; “mRR\((sup-std)\)” \((r=0.448, p<0.05)\). However HbA1c had no correlation with these parameters of autonomic nerve function and blood pressure rise at tracheal intubation. Because of above correlation with blood pressure rise at intubation for anesthesia induction, the preoperative fructosamine examination and the responsive sympathetic nerve function test must be useful preoperative examination for detection of the un-
expected heart events of diabetic patients during operation.——
fructosamine; sympathetic activity; heart rate variability; diabetes mellitus;
anesthesia  © 1999 Tohoku University Medical Press

In performing surgical operations on cases with diabetes mellitus, it is
difficult to predict accurately the risk of intraoperative hemodynamic changes, in
spite of having a high risk including the cardiovascular system in general (Ewing
et al. 1976). Furthermore we anesthetists must avoid the blood pressure (BP)
change of up and down during anesthesia.

Changes of blood pressure in response to some stimulation are regulated
through the autonomic nervous system. Patients with diabetes mellitus of a
longer standing develop various complications of neuropathy, especially disorders
of autonomic nervous activity (Burgos et al. 1989). Therefore, surgical opera-
tions on diabetics who have complications of autonomic nervous disorder may be
expected to carry associated risks in some cases, which case reports have suggested
the diabetic patients undergoing surgery may have a higher incidence of undesir-
able cardiovascular events than the general population (Garcia et al. 1974;
Palumbo et al. 1976; Knuttgen et al. 1990). These cases were often noted retro-
spectively to have severe autonomic neuropathy (Ciccarilli et al. 1986; Niakan et
al. 1986; Triantafillou et al. 1986).

In the present prospective study, we examined diabetic patients having
greater risk of cardiovascular events during anesthesia and surgery 1) to determine
if preoperative autonomic test which were assessed heart rate variability (HRV)
analysis might be used to predict the blood pressure changes relating to tracheal
stimulation by intubation/extubation for anesthesia, 2) to determine which
preoperative biochemical assays, the blood level of fructosamine reflecting the
blood plasma glucose level or hemoglobin A1c (HbA1c), might be useful to predict
the blood pressure changes relating to tracheal intubation.

Subjects and Methods

Subjects and their preoperative biochemical assay

The subjects studied were 24 non-insulin dependent diabetic patients in
whom HbA1c and fructosamine levels were measured preoperatively. The
preoperative biochemical assays of the 24 diabetics in average were following
(Mean ± s.d.): HbA1c; 7.4 ± 1.5%, fructosamine; 312.6 ± 64.7 μmol/liter. The
patients studied in this time did not have any heart disease.

Preoperative test of autonomic nerve function

Autonomic activity was quantified by analysis of ECG R-R variability.
ECG R-R signals were recorded preoperatively in supine and a subsequent
standing position, under constant respiratory frequency of 15/minutes utilized an
HRV analyzer (FUKUDA DENS1 Co., Tokyo) for this purpose. Those signals at
1024 points respectively were put to A/D converter and analyzed by various non-spectral procedures automatically. In frequency analysis by Fast Fourier transform (FFT), the 0.03-0.4 Hz frequency band was used as total power (TP) component and low frequency (LF) and high frequency (HF) area were defined each as 0.03-0.15 and 0.15-0.4 Hz. As the parameters of autonomic activities from the HRV analysis, we availed the non-spectral statistical and spectral analysis values showed following: (a) The mean value of R-R interval in supine during 200 heart beats showed as a symbol of “mRR(sup)”, which means parasympathetic dominance on more than standard value. (b) The coefficient of variation (CV_{RR}) in supine is used as vagal or parasympathetic parameter. (c) The difference between the mRR(sup) and minimum R-R interval to subsequent standing position; showed as symbol of “mRR(sup)-RRmin(std)” which means bigger sympathetic irritability on more than standard value (Goto et al. 1998) (Fig. 1). (d) The difference between the mRR(sup) and mRR(std) showed as symbol of “mRR(sup-std)” which means bigger sympathetic excitability on more than standard value (Goto et al. 1998) (Fig. 1). (e) The low frequency component to total power component ratio in standing position; “LF/TP(std)” are used as the sympathetic index (Goto et al. 1994).

Above standard values of autonomic parameters have been reported and used from the data which were obtained from the 100 young healthy (24 ± 1.3 year old) (Goto et al. 1994).

Anesthesia managements

Anesthesia was induced under premedication of atropine sulfate 0.006 mg · kg^{-1} of thiopental and 50% N_{2}O, 0.2 mg · kg^{-1} of vecuronium was used, and 0-1.5% isoflurane was added for maintenance of anesthesia after intubation. During surgery, blood pressure was measured with an automatic sphygmomanometer (NIHON COLIN Co., Tokyo) to monitor its changes due to the autonomic nervous reflex produced by tracheal stimulation of intubation/extubation for general anesthesia. The surgical time needed for operation were 350 minutes in average (3-8 hours), and we did a similar conditioned 24 non-diabetic patients of the time required for surgical operation with contrast retrospectively.

Statistical analysis

Statistical analysis was performed by Statview 4.11, and statistical significance tested by unpaired t-test at the level of p < 0.05.

Results

Systolic blood pressure changes at intubation and extubation for anesthesia

The mean percentage changes in systolic blood pressure (sBP) induced by stimulation of tracheal intubation in 40 diabetic patients and another 40 non-diabetic patients are compared retrospectively in Table 1. The percentages of its
Fig. 1. Indices of sympathetic activities from R-R variability. 
Upper wave of each Figs. is R-R interval variation in supine, and under wave is in standing subsequent after supine. A starting parts of wave level in standing show a remarkable down, that is, make responsive tachycardia due to stimulate of sympathetic system, an index of so called “sympathetic irritability” that is the difference between the mean value of R-R interval variation in supine and its minimum level of wave in standing.(A) Besides, the wave of continuous sympathetic stimulation in standing is shown by its mean value of “mRR(std),” therefore the difference between these two mean values is an index of so called “sympathetic excitability”.(B)

 increases due to tracheal stimulation at intubation and afterdrop at 5 minutes were almost same in both groups of about 20% and 30%, respectively.

The mean % blood pressure increases at extubation was also indicated no difference between the two groups, but the blood pressure drops at 5 minutes after extubation was larger in the diabetic group (9.7%) than the non-diabetic group

<p>| Table 1. Systolic blood pressure at intubation and extubation for general anesthesia |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>Age</th>
<th>Pre-</th>
<th>at intubation (%) increase</th>
<th>after 5 minutes (%) drop</th>
<th>pre</th>
<th>at extubation (%) increase</th>
<th>after 5 minutes (%) drop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics</td>
<td>40</td>
<td>61.0</td>
<td>134.0</td>
<td>159.6 ± 24.3 (20.4%)</td>
<td>107.5 ± 15.4 (21.4%)</td>
<td>138.7 ± 26.3 (17.3%)</td>
<td>161.1 ± 26.7 (17.3%)</td>
<td>144.2 ± 20.1 (−9.7%)</td>
</tr>
<tr>
<td>Non-diabetics</td>
<td>40</td>
<td>57.3</td>
<td>130.4</td>
<td>157.0 ± 24.3 (21.0%)</td>
<td>105.3 ± 15.1 (21.5%)</td>
<td>125.1 ± 21.5 (18.4%)</td>
<td>146.6 ± 19.3 (−5.9%)</td>
<td>137.4 ± 19.3 (−5.9%)</td>
</tr>
</tbody>
</table>

Mean ± s.d. (mmHg)
(5.9%) (Table 1).

Correlation of blood pressure changes with autonomic nervous activity

No correlation was found with % blood pressure increase at intubation / extubation and each parameter of preoperative autonomic nervous activity. But there were some correlation with % blood pressure drops at 5 minutes after intubation/extubation.

In a diabetic patient with lower vagal nerve activity; “CV_{RR},” the % blood pressure drops after intubation was significantly larger (r = 0.513, p < 0.001) and in a non-diabetic patient with higher sympathetic nerve excitability; “mRR(sup-std),” the % blood pressure drops at 5 minutes after extubation was significantly larger (r = 0.502, p < 0.001) (Fig. 2).

Preoperative fructosamine level and sympathetic nerve activity in diabetics, and sBP changes at intubation for anesthesia

In cases with more higher fructosamine levels in diabetics, the parameters of responsive sympathetic nerve function, that is, the sympathetic irritability; “mRR(sup)-RRmin(std),” and the sympathetic excitability; “mRR(sup-std)” become larger (r = 0.432 and 0.448, p < 0.05, respectively) (Fig. 3).

The parameter of vagal nerve function and the relative sympathetic activity; “LF/TP(std)” have no correlation with fructosamine levels at all. HbA1c levels, on the other hand, showed no correlation at all with any of the indices (Table 2).

Discussion

Many diabetic patients may have a high risk including the cardiovascular system. Some hidden factor or other which cannot be specifically checked before a surgical operation may be conceivable. In particular, the dangerous risk becomes high in an advanced age of 60 year old or more. Accordingly BP change in the induction of anesthesia will be raised this risk. A mechanical stimulation to airway by tracheal intubation is most radically at the larynx (Widdicombe 1954). Furthermore, the operation of a laryngoscopy and intubation will cause the laryngeal or upper airway reflexes (Seagard et al. 1984). The stimuli transmit to a medullar center via centripetal vagal nerve pathway, and reflected centrifugal vagal and/or sympathetic nerve control to cardiac rhythm via cardiovascular center becomes blood pressure change in tracheal intubation. However, in diabetics, a disturbance of vagal nervous function is said to proceed that of sympathetic nervous function in generally (Pfeifer et al. 1982; Oikawa et al. 1986).

Since frequency domain analysis of R-R interval variability was introduced by Sayer (1973), this method has become a good measure to study autonomic cardiac outflow to the heart because this approach may provide quantitative information on the level of sympathetic- as well as vagal-cardiac neural outflow.
Fig. 2. Relationship with BP afterdrop at intubation/extubation and preoperative autonomic nervous function.

(A), Blood pressure drop after intubation vs. vagal nerve activity in diabetics. 
\[ Y = -44.14 + 4.66X \quad r = 0.513 \quad (p < 0.001) \]

(B), Blood pressure drop after extubation vs. sympathetic excitability in non-diabetics. 
\[ Y = 4.66 - 0.07X \quad r = 0.502 \quad (p < 0.001) \]

Spectral analysis of R-R interval or heart rate in a variety of physiological settings has been shown to provide indicators of sympathetic nervous system and parasympathetic nervous system activities.

The biochemical assay relating to blood glucose metabolism in diabetic patients has often focused only on the evaluation of blood glucose values. In recent years, HbA1c, glucose-bound hemoglobin, has been known to be a good index which roughly indicates the status of controlled blood glucose level for the past one to two months. Because HbA1c reflects the past averaged blood glucose level in long-standing diabetic patients, it is naturally conceivable which it may have to do with disturbance of autonomic nervous activity. However, Yamasaki et al. (1991), who studied HRV in healthy subjects and diabetic patients by power spectral analysis, described that the LF component increased in healthy subjects due to tilting but did not do so in diabetic patients, that the HF component
Fructosamine and ANF in DM and Anesthesia

Fig. 3 Relationship with preoperative fructosamine level and the preoperative sympathetic activity. A diabetics with more higher level of fructosamine has high sympathetic activity.

(A), vs. mRR(sup)-RRmin(std) \( Y = 73.09 + 0.39X; r = 0.432 \ p < 0.05 \).

(B), vs. mRR(sup-std) \( Y = 10.527 + 0.378X; r = 0.448 \ p < 0.05 \).

Table 2. Coefficient of correlation (r) between Fructosamine, HbA1c, and six indices of autonomic nerve function

<table>
<thead>
<tr>
<th>Index of autonomic nerve function</th>
<th>Fructosamine</th>
<th>HbA1c</th>
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<tbody>
<tr>
<td>mRR (sup)</td>
<td>0.374*</td>
<td>0.185</td>
</tr>
<tr>
<td>SD_{RR} (sup)</td>
<td>0.175</td>
<td>0.035</td>
</tr>
<tr>
<td>CV_{RR} (sup)</td>
<td>0.117</td>
<td>0.072</td>
</tr>
<tr>
<td>mRR (sup-std)</td>
<td>0.448*</td>
<td>0.074</td>
</tr>
<tr>
<td>mRR (sup)-RRmin (std)</td>
<td>0.432*</td>
<td>0.200</td>
</tr>
<tr>
<td>LF/T.P (std)</td>
<td>0.316</td>
<td>0.049</td>
</tr>
</tbody>
</table>

\*p < 0.05,  \*\*p < 0.1
increased in mild diabetic patients with no neuropathy as in healthy subjects, and that these parameters of autonomic nerve function had no relation to HbA1c at all.

In our study as well, HbA1c values had no correlation to any of the parameters of autonomic nerve function studied. However, the fructosamine level in diabetic patients took up in this study was shown to have correlated with autonomic nerve function. Namely, in diabetic patients with higher fructosamine levels, specially there was the large correlation with acceleration of the responsive sympathetic irritability, quantified in subsequent standing position from supine. These data suggest that the diabetic patients with higher fructosamine levels may have high cardiovascular risks easy irritable or excitable to even the slightest stimulation due to have high sympathetic activity. It is considerable that the cardiovascular change will be have relation with autonomic nerve function of patient.

In the present study, there are a little BP rise at intubation, but great fall down immediately after BP rise in average. It is considered that a control of autonomic regulation will weaken by some depression of sympathetic activity in older. The non-diabetic patient scheduled operation are older (59.0±11.1 year old) than criterion person (24.0±1.3 year old) and sympathetic activities were generally low. But in case of diabetics (61.9±9.1 year old), the regulating control ability of the sympathetic activity was different from non-diabetics in spite of almost same age. Above facts show that a diabetic patients have some autonomic nerve disturbance.

When an individual value was analyzed apart from the above group comparison by average, it was found that the fructosamine concentration considerably correlated with blood pressure changes at intubation, that is, a diabetic patient with higher fructosamine levels may have had a certain correlation with some index of autonomic nerve function.

The data of this study that fructosamine has more large influence to autonomic nervous function than HbA1c will suggest that the glucose combined with serum protein immerse the nerve tissues more directly than the glucose combined with hemoglobin in red cells, and may cause more severe nerve disturbances.

It has been reported that the blood levels of norepinephrine in diabetic patients are below normal range (Eckberg et al. 1986), and there are abnormalities in the pathways of the autonomic nervous system and baroreceptor reflex (Tsueda et al. 1991; Bodmer et al. 1994) and that conductivity of stimuli is lowered in the central nervous system as well (Donald et al. 1984). These findings suggest that the diabetic patients will be insensible to rise sympathetic function reflectively against every stimuli than the non-diabetics. There is a certain relationship between severity of neuropathy and hemodynamic change during anesthesia for surgery. Because of the central nervous function will not be depressed completely yet by anesthetics at intubation period, no difference was found between two
groups in the blood pressure increase at intubation, but in diabetics with vagal
nerve disturbance, the afterdrop of blood pressure at intubation was found. On
the other hand, at extubation period, the depression of the central nervous
function will be continued. However the recovery of autonomic nervous func-
tion from anesthesia may be more usual in non-diabetics essentially. Therefore
the % blood pressure drop after extubation was larger in non-diabetics with high
sympathetic nervous activity.

Still more, our study suggest a possibility of foreknowing of these danger by
means of preoperative screening tests of sympathetic nerve activity and
fructosamine measurement. The blood level of fructosamine, a type of
glycosylated protein albumin, reflects the blood glucose level for a shorter time
than HbA1c does, that is, over the past two weeks, and, unlike blood glucose, is
not affected by food intake. For this reason, a clinical examination test of
fructosamine level as well as autonomic nerve function availed heart rate variabil-
ity are more suitable and more practicable as a test before an operation.

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