Abstract

Plasma N-terminal Pro-Brain Natriuretic Peptide (Nt-proBNP) level has been shown to provide valuable prognostic information on short and long-term mortality in patients with acute Myocardial Infarction, in the general population. Increased plasma Nt-proBNP levels have been found in Type 2 diabetic patients with vascular complications or with hypertension. In a large prospective study performed in 560 patients hospitalized for acute Myocardial Infarction (RICO), we found that median Nt-proBNP levels were significantly higher in the 199 diabetic patients compared to the 361 non-diabetic patients (245 (81-77) vs. 130 (49-199) pmol/L, \(P<0.0001\)). This difference remained highly significant after adjustment for confounding factors and we have been able to show that diabetes, per se, was a strong and independent factor for increased plasma Nt-proBNP levels, in this population. In the prospective RICO survey, we have found, in multivariable analysis, that diabetes was an independent factor for in-hospital mortality (OR: 1.79 (1.45-2.20); \(P=0.0064\)) and cardiogenic shock (OR: 1.45 (1.22-1.72); \(P=0.0364\)) when the variable Nt-proBNP level was not introduced into the model, but was less significantly associated with mortality (OR: 1.73 (1.39-2.16); \(P=0.0107\)) and no longer associated with cardiogenic shock when Nt-proBNP was in the model. This data suggest that increased plasma Nt-proBNP may be one of the links between diabetes and poor short-term prognosis after Myocardial Infarction and provides highly valuable prognostic information on in-hospital outcome in diabetic patients.

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Résumé

Concentrations plasmatiques de Nt-proBNP et pronostic après infarctus du myocarde au cours du diabète

Dans la population générale, le taux plasmatique de N-terminal Pro-Brain Natriuretic Peptide (Nt-proBNP) est un indice du pronostic à court et long terme après infarctus du myocarde. Des taux augmentés de Nt-proBNP ont été rapportés chez des patients diabétiques de type 2 avec atteinte cardiovasculaire ou hypertension artérielle. Dans une étude prospective de grande taille réalisée chez 560 patients hospitalisés pour infarctus du myocarde (RICO), nous avons observé que le taux médian de Nt-proBNP était significativement plus élevé chez les 199 patients diabétiques que chez les 361 patients non diabétiques (245 (81-77) vs. 130 (49-199) pmol/L, \(P<0.0001\)). Cette différence demeurait hautement significative après ajustement pour les facteurs confondants et nous avons pu montrer que le diabète, per se, était, dans cette population, un puissant facteur indépendant de l’augmentation des taux plasmatiques de Nt-proBNP. Dans cette même étude RICO, nous avons montré qu’en analyse multivariée, le diabète était un facteur indépendant de mortalité hospitalière (OR: 1.79 (1.45-2.20); \(P=0.0064\)) et de choc cardiogénique (OR: 1.45 (1.22-1.72); \(P=0.0364\)), lorsque la variable Nt-proBNP n’était pas prise en compte. Mais, lorsque la variable Nt-proBNP était introduite dans le modèle statistique, l’association indépendante entre le diabète et le choc cardiogénique n’était plus retrouvée et celle entre le diabète et la mortalité hospitalière était moins importante (OR: 1.73 (1.39-2.16); \(P=0.0107\)). Ces données
montrent que le Nt-proBNP est un excellent indice du pronostic à court terme après infarctus du myocarde, chez les patients diabétiques et qu’il pourrait être un des liens entre le diabète et le mauvais pronostic après nécrose myocardique.

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**Keywords:** Diabetes; Myocardial infarction; Nt-proBNP; BNP; Ischemia

**Mots clés :** Diabète ; Infarctus du myocarde ; Nt-proBNP ; BNP ; Ischémie

Brain Natriuretic Peptide (BNP) and N-terminal Pro-Brain Natriuretic Peptide (Nt-proBNP) are secreted from cardiomyocytes in response to increased wall stress [1-4]. BNP is produced as a 108 amino acid prohormone, proBNP, which is enzymatically cleaved into the 32 amino-acid BNP and the N-terminal part of the prohormone, Nt-proBNP [4]. Levels of BNP and Nt-proBNP correlate with left ventricular dilatation, remodeling and dysfunction in patients after acute Myocardial Infarction [5, 6]. In patients with acute Myocardial Infarction, the increase in Nt-proBNP is greater than in BNP [7] and has a higher discriminative value for early cardiac dysfunction than BNP, suggesting it may be a more sensitive marker of left ventricular dysfunction [8-9]. Plasma Nt-proBNP level has been shown to provide valuable prognostic information on short and long-term mortality in patients with acute Myocardial Infarction [5, 9]. It has recently been shown that Nt-proBNP was independently associated with the risk of sudden death in patients with heart failure [10].

**1. Nt-proBNP in Type 2 diabetes**

Levels have been found increased in Type 2 diabetic patients with vascular complications [11]. In this study, coronary heart disease and nephropathy (defined as an albumin/creatinine ratio above 2 mg/mmol) were each independently associated with elevated values of Nt-proBNP. In a study performed in 60 Type 2 diabetic patients without albuminuria, mean Nt-proBNP level was significantly higher among diabetic hypertensive patients compared with both diabetic normotensive patients and controls but no difference was found between the diabetic normotensive patients and the controls [12]. In this study, diabetic patients with concentric and eccentric hypertrophy or left atrial enlargement had significantly higher Nt-proBNP levels compared with the control group and the increased plasma level of Nt-proBNP observed in hypertensive, normoalbuminuric patients with Type 2 diabetes was related to left ventricular hypertrophy and increased left atrial and ventricular diameters [12]. An echocardiographic study has shown that plasma Nt-proBNP level was elevated in type 2 diabetic patients with normal ejection fraction but with diastolic dysfunction [13]. In a cross-sectional study, it has been shown that median plasma Nt-proBNP was increased in diabetic patients without overt cardiovascular disease suggesting a higher prevalence of asymptomatic left ventricular dysfunction [14]. In a study performed in 560 patients hospitalized for acute Myocardial Infarction, we found that median Nt-proBNP levels were significantly higher in the 199 diabetic patients compared to the 361 non-diabetic patients (245 (81-77) vs. 130 (49-199) pmol/L, P<0.0001) [15]. This difference remained highly significant after adjustment for age, female gender, creatinine clearance, left ventricular ejection fraction (LVEF), plasma peak troponin, anterior wall necrosis and hypertension [15]. We performed a multivariable linear regression analysis to analyze the association between plasma Nt-proBNP and several variables known to be associated with Nt-proBNP. The variables introduced into the model were those which were associated with Nt-proBNP with a p value < 0.20, in the univariate analysis: creatinine clearance, plasma peak troponin, LVEF, age, gender, diabetes, hypertension, anterior wall necrosis and ST segment elevation Myocardial Infarction (STEMI). The multivariable analysis showed that Nt-proBNP was negatively associated with creatinine clearance (P<0.0001) and LVEF (P<0.0001) and positively associated with plasma peak troponin level (P<0.0001), age (P=0.0016), diabetes (P=0.0045) and female gender (P=0.0104), but neither with hypertension, anterior wall necrosis nor STEMI [16]. When multivariable regression analysis was performed in the subgroup of diabetic patients with Myocardial Infarction, Nt-proBNP was negatively associated with creatinine clearance (P=0.0004) and LVEF (P=0.0003) and positively associated with peak plasma troponin level (P=0.0002), mean fasting blood glucose (P=0.0281) and female gender (P=0.0375) [15].

Increased plasma levels of Nt-proBNP have been reported in diabetic patients without overt cardiovascular disease [14, 16] and with acute coronary syndrome [17]. However, no adjustment for LVEF, an important determinant of plasma Nt-proBNP have been performed in these studies. In our study, we found a significant increase in plasma Nt-proBNP in diabetic patients compared to non-diabetic patients independently of possible confounders such as age, sex, LVEF, creatinine clearance, BMI, hypertension, plasma troponin level and anterior wall location. Our data suggest that diabetes, per se, is a strong and independent factor for plasma Nt-proBNP after Myocardial Infarction. Interestingly, we found a 88% increase in Nt-proBNP median value in diabetic patients after Myocardial Infarction when only a 20% increase was observed by Magnusson et al in diabetic patients without overt cardiovascular disease [14], suggesting a strong influence of diabetes on plasma Nt-proBNP level in acute coronary events.
2. Nt-proBNP and short term prognosis after Myocardial Infarction, in Type 2 diabetes

RICO survey, a registry of patients hospitalized for acute Myocardial Infarction in one eastern region of France, were studied prospectively. Among the 560 patients, 199 (35%) were diabetic. During the hospital stay, mortality was significantly higher in diabetic patients than in non-diabetic patients (15.6% vs. 3.3%, P<0.0001). A significant 2.2 fold increase in cardiogenic shock was observed in the diabetic group compared to the non-diabetic group (17.6% vs. 7.7%, P=0.0004). No significant differences were noted between diabetic and non-diabetic patients for recurrent Myocardial Infarction (12.1% vs. 8.3%, P=0.23) (Fig. 1). Plasma Nt-proBNP levels were significantly higher in patients who died at hospital (800 (147-3915) vs. 143 (55-357) pMol/L P<0.0001) and in those who suffered a cardiogenic shock during in-hospital stay (680 (164-1577) vs. 137 (53-336) pMol/L, P<0.0001) (Fig. 2).

In multivariate analysis, cardiogenic shock was associated with systolic blood pressure (mm Hg)(OR: 0.96(0.95-0.97); P<0.0001), creatinine clearance <60 ml/min (OR: 1.54 (1.30-1.82); P=0.0125) and diabetes (OR: 1.45(1.22-1.72); P=0.0364), when Nt-proBNP was not introduced into the model. When Nt-proBNP was introduced into the model, cardiogenic shock was associated with Nt-proBNP (OR: 2.22 (1.92-2.58); P<0.0001), systolic blood pressure (OR: 0.96(0.95-0.97); P<0.0001) but no longer with diabetes (Table 1).

In multivariable analysis, diabetes was an independent factor for mortality (p=0.0064) when the variable Nt-proBNP was not introduced into the model, but was less significantly associated with mortality (P=0.0107), when Nt-proBNP was in the model (Table 2).

Our findings are consistent with the previous data showing an increased incidence of cardiogenic shock and in-hospital mortality after Myocardial Infarction, in diabetic patients [18, 19]. Moreover, we found a strong association between plasma Nt-proBNP level and the level of risk for death or cardiogenic shock after Myocardial Infarction, in patients with diabetes. This is a major finding of our study, as it suggests that increased plasma Nt-proBNP may be one of the links between diabetes and the increased risk for cardiogenic shock after Myocardial Infarction. Indeed, in multivariable analysis, diabetes is a significant independent factor for cardiogenic shock when the variable Nt-proBNP is not introduced into the model but is no more associated with increased risk of cardiogenic shock when Nt-proBNP is introduced into the model. This result supports the hypothesis that the increased risk of both cardiogenic shock and in-hospital mortality after Myocardial Infarction in diabetic patients is linked to elevated Nt-proBNP levels.

Plasma Nt-proBNP reflects not only the size of the myocardial necrosis but also the extent of ischemic territory [9, 20]. Indeed, plasma Nt-proBNP is increased in patients with acute coronary syndrome, even in the absence of necrosis [9, 21]. Plasma Nt-proBNP elevation is also associated with renal impairment, hypertension and systolic dysfunction [5, 9, 16, 17] and seems to reflect the integral of different risk markers for adverse outcomes following Myocardial Infarction with a high informative value.

Several pathophysiological mechanisms might explain the increase in plasma Nt-proBNP after Myocardial Infarction, in diabetic patients. Diabetic patients, even those who are asymptomatic for cardiovascular disease, have frequent and early echographic abnormalities including increased...
### Table 1
Predictor of cardiogenic shock by multivariable logistic regression analysis.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef.</th>
<th>SD</th>
<th>Wald</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (without Nt-proBNP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-0.04</td>
<td>0.007</td>
<td>31.70</td>
<td>0.96 [0.95-0.97]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60 ml/min (vs ≥ 60 ml/min)</td>
<td>0.43</td>
<td>0.17</td>
<td>6.24</td>
<td>1.54 [1.30-1.82]</td>
<td>0.0125</td>
</tr>
<tr>
<td>Diabetes (vs no diabetes)</td>
<td>0.37</td>
<td>0.17</td>
<td>4.38</td>
<td>1.45 [1.22-1.72]</td>
<td>0.0364</td>
</tr>
<tr>
<td>Non significant variables (removed from the model): age (p=0.50), Diastolic Blood pressure (P=0.96) and history of MI (vs no history of MI) (p=0.10).</td>
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<tr>
<td>Model 2 (with Nt-proBNP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nt-proBNP (log) (pMol/L)</td>
<td>0.80</td>
<td>0.15</td>
<td>26.94</td>
<td>2.22 [1.92-2.58]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-0.037</td>
<td>0.007</td>
<td>25.38</td>
<td>0.96 [0.95-0.97]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non significant variables (removed from the model): age (p=0.10), Diastolic Blood pressure (p=0.86), history of MI (vs. no history of MI) (0.52), creatinine clearance &lt;60 ml/min (vs. ≥ 60 ml/min) (0.40) and Diabetes (vs. no diabetes)(0.47).</td>
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</table>

### Table 2
Predictor of mortality by multivariable logistic regression analysis.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coef.</th>
<th>SD</th>
<th>Wald</th>
<th>OR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (without Nt-proBNP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance &lt;60 ml/min (vs ≥ 60 ml/min)</td>
<td>1.07</td>
<td>0.23</td>
<td>21.97</td>
<td>2.91 [2.31-3.66]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-0.02</td>
<td>0.007</td>
<td>9.18</td>
<td>0.98 [0.97-0.99]</td>
<td>0.0024</td>
</tr>
<tr>
<td>Diabetes (vs no diabetes)</td>
<td>0.58</td>
<td>0.21</td>
<td>7.44</td>
<td>1.79 [1.45-2.20]</td>
<td>0.0064</td>
</tr>
<tr>
<td>Heart rate at admission (log) (10 pulses/min)</td>
<td>0.360</td>
<td>0.18</td>
<td>3.98</td>
<td>1.43 [1.19-1.71]</td>
<td>0.0461</td>
</tr>
<tr>
<td>Non significant variables (removed from the model): age (0.96), Diastolic Blood pressure (P=0.56), history of MI (vs no history of MI) (0.64), anterior wall location (vs other location) (0.89), female gender (vs male) (0.30) and STEMI (vs non STEMI) (0.54).</td>
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<td></td>
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<tr>
<td>Model 2 (with Nt-proBNP)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nt-proBNP (log) (pMol/L)</td>
<td>0.82</td>
<td>0.25</td>
<td>10.93</td>
<td>2.27 [1.77-2.91]</td>
<td>0.0009</td>
</tr>
<tr>
<td>Creatinine clearance &lt;60 ml/min (vs ≥ 60 ml/min)</td>
<td>0.42</td>
<td>0.15</td>
<td>7.18</td>
<td>1.52 [1.31-1.77]</td>
<td>0.0073</td>
</tr>
<tr>
<td>Diabetes (vs no diabetes)</td>
<td>0.55</td>
<td>0.22</td>
<td>6.51</td>
<td>1.73 [1.39-2.16]</td>
<td>0.0107</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>-0.017</td>
<td>0.007</td>
<td>5.75</td>
<td>0.98 [0.97-0.99]</td>
<td>0.0165</td>
</tr>
<tr>
<td>Non significant variables (removed from the model): age (0.48), Diastolic Blood pressure (P=0.35), history of MI (vs no history of MI) (0.33), anterior wall location (vs other location) (0.96), female gender (vs male) (0.58), STEMI (vs non STEMI) (0.57) and heart rate at admission (log) (pulse/min) (0.10).</td>
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</tbody>
</table>

MI: Myocardial infarction; STEMI: ST segment Elevation MI
myocardial stiffness, impaired left ventricular compliance and diastolic dysfunction [22, 23]. ATP deficiency may be responsible for the early myocardial dysfunction observed in diabetes. Indeed, diabetic patients have an intracellular glucose deficiency leading to impaired production of ATP, which does not allow adequate Na⁺/K⁺-ATPase and Ca²⁺-ATPase functions. This modification of ion pumps leads to impaired relaxation in the myocardium [24], which could account for the increased Nt-proBNP secretion. Such metabolic features for increased Nt-proBNP levels in diabetes could also explain the independent association between fasting glycaemia and Nt-proBNP levels found in our study. Moreover, the increased collagen content observed in hearts from diabetic patients is responsible for increased myocardial stiffness and may participate to the elevation of plasma Nt-proBNP in diabetes [25]. In addition, the elevated plasma Nt-proBNP levels, observed in diabetic patients after Myocardial Infarction, may also be explained by the more severe ischemia, compared to non-diabetic patients, even with a similar infarct size. Indeed, autopsic data have shown a lower capillary density in the myocardium of diabetic patients who died from Myocardial Infarction, which could partly explain the severity of ischemia [26]. Furthermore, endothelium dysfunction, which has been reported in diabetic patients, could also be involved in the extent of ischemia [27].

Nt-proBNP and long term prognosis after Myocardial Infarction, in Type 2 diabetes

So far, no specific study analyzing the relationship between plasma Nt-proBNP and long-term prognosis after Myocardial Infarction has been performed. However, two studies have examined the prognostic value of Nt-proBNP in patients with Type 2 diabetes [28, 29]. Gaede et al. have investigated the association between plasma Nt-proBNP and cardiovascular disease in the 160 microalbuminuric type 2 diabetic patients enrolled in the Steno 2 study [28]. In this study, plasma Nt-proBNP being above the median was associated with an increased risk of cardiovascular disease (primary endpoint including cardiovascular mortality, non fatal myocardial infarction, non fatal stroke, PCI, CABB, vascular surgery and amputations) during the 7.8 year follow-up with an unadjusted hazard ratio of 4.4 (95% CI 2.3-8.4, P<0.0001) and hazard ratio of 3.6 (1.7-7.5, P=0.001) after adjustment for other cardiovascular risk factors [28]. In a prospective 15.5 year follow-up study, Tarnow et al. examined the relationship between baseline plasma Nt-proBNP level and cardiovascular mortality [29]. All-cause mortality was increased in patients with Nt-proBNP in the second and third tertiles (hazard ratios [95% CI] compared with the first tertile, 1.70 [1.08-2.67] and 5.19 [3.43-7.88], P<0.001). This association persisted after adjustment for urinary albumin excretion rate, glomerular filtration rate and conventional cardiovascular risk factors for the third tertile (covariate adjusted hazard ratios 2.54 [1.56-4.14], P<0.001). This increased mortality was attributable to more cardiovascular deaths. Thus, it seems that, in patients with Type 2 diabetes, Nt-proBNP is a strong predictor of cardiovascular disease and mortality, independently of urinary albumin secretion rate and conventional cardiovascular risk factors.

No potential conflict of interest reveal to this article was reported.

References


