Effect of exposure to second-hand smoke on serum levels of N-terminal pro-brain natriuretic peptide

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Background and objectives
Exposure to second-hand smoke is as hazardous as exposure to first-hand smoke, and can cause cardiovascular disease. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a valid negative biomarker of left ventricular (Lv) dysfunction. The current study investigated the effect of exposure to second-hand smoke on serum levels of NT-proBNP, aiming to use NT-proBNP as a screening tool of Lv dysfunction in passive smokers.

Participants and methods
A total of 60 passive smokers and 20 matched controls were enrolled in the study; their ages range from 20 to 35 years. History of cardiovascular or pulmonary disease was an exclusion criterion. Demographic, anthropometric, and passive smoking data were collected through a self-administered questionnaire and physical examination. The extent of passive smoking was assessed by calculating the pack per year history. Serum levels of NT-proBNP were measured using an electrochemiluminescence assay for each participant.

Results
Analysis of data showed that passive smokers were currently exposed to second-hand smoke, 91.7% were living with the smoker, and 8.3% smoker's colleagues. Serum levels of NT-proBNP were 251.2 ± 46.9 and 148.3 ± 29.7 pg/ml in passive smokers and controls, respectively. Also, there was a significant difference ($P < 0.0001$, 105.4 ± 11.64) in serum NT-proBNP between passive smokers and controls. Serum NT-proBNP was correlated with both the duration and the amount of exposure to second-hand smoke ($r = 0.313$ and 0.763, $P = 0.015$ and 0.0001, respectively).

Interpretations and conclusion
These results showed that exposure to second-hand smoke could increase serum levels of NT-proBNP. Accordingly, an elevated NT-proBNP could be a strong predictor of Lv dysfunction in passive smokers.

Keywords:
BNP, exposure, left ventricular dysfunction, N-terminal pro-B-type natriuretic peptide, passive smokers, second hand

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Introduction

Despite the ongoing worldwide smoking pan campaigns, complications of smoking remain a major health problem worldwide. Individuals exposed to second-hand smoke inhale the side stream smoke, which has been found to contain higher concentrations of the same chemicals and carcinogens present in mainstream smoke [1]. According to the WHO, tobacco kills around six million individuals a year worldwide, including more than 600 000 nonsmokers who die from exposure to second-hand smoke. Since 1964, 2.5 million Americans have died from cardiovascular and pulmonary disease because of passive smoking [2].

Assessment of left ventricular (Lv) dysfunction relies mainly on ECG and echocardiographic changes. ECG changes are late and nonspecific [3]. However, echocardiography is not available in all healthcare centers as it is expensive and requires a highly skilled sonographer. Accordingly, it cannot be considered a screening tool for Lv dysfunction [4].

The B-type natriuretic peptide is a hormone produced by the Lv myocytes in response to ventricular stretch [5]. The N-terminal pro-B-type natriuretic peptide (NT-proBNP) is the inactive amino terminal of BNP that lives for 60–120 min. Both BNP and NT-proBNP have been found to be increased in various cardiovascular disorders. Owing to its longer half-life, NT-proBNP was proposed by others as a biomarker for cardiovascular abnormalities [6].

NT-proBNP has been studied extensively in health problems other than cardiovascular disease. The pathophysiology of these disorders was directly or indirectly linked to ventricular dysfunction. The most common is pulmonary disorders, where BNP was not only found to be elevated but was also a strong predictor of mortality in these disorders [7].

In 2010, Otsuka and colleagues reported that serum levels of NT-proBNP in current smokers are higher than normal in the absence of overt cardiovascular disease [8]. To our knowledge, this is the first study to investigate the effect of exposure to second-hand smoke in serum NT-proBNP.

Participants and methods

Study design and study populations

A case–control study was carried out at El-Fayoum General Hospital, at El-Fayoum governorate, Egypt, in the period from June 2013 to April 2014. Sixty passive smokers were recruited from among companions of patients attending the outpatient clinics of the hospital. Twenty sex-matched and age-matched healthy volunteers were also enrolled in the study; these were physicians and coworkers. The absence of a medical history of cardiovascular or pulmonary disease was an important inclusion criterion. The sample size was determined according to the availability of biochemical determination of NT-proBNP.

Methods of data collection

A self-administered questionnaire was distributed to each participant. Questions aimed to collect demographic, clinical, and passive smoking data. The amount of second-hand smoke inhaled was assessed by calculating pack per year history of passive smoking (mimicking) and the standard pack per year history of smoking [9]. This was achieved by multiplying the duration of exposure to second-hand smoke in years by the approximate number of cigarettes smoked by the active smoker for each exposure per day. Then, the resulting number was divided by 20. Then, each participant was subjected to a detailed clinical examination, including measurement of systolic blood pressure (SBP) using a mercurial sphygmomanometer. Assessment of body weight was also performed using a Detecto scale.

N-terminal pro-B-type natriuretic peptide analysis

Venous blood was collected in plain tubes, incubated at 37°C for 10–15 min, and then centrifuged at 3000 rpm to separate serum. Serum NT-proBNP was assessed using an electrochemiluminescence assay (Elecsys proBNP; Roche Diagnostics, Manheim, Germany) following the manufacturer's instructions. The range of detection was from 5 to 35 000 pg/ml. For descriptive purposes, serum levels of NT-proBNP were classified into three ranges: normal 5–250 pg/ml, high normal 251–300 pg/ml, and high more than 300 pg/ml.

Statistical analysis

The collected data were analyzed using the SPSS 17.0 software for windows (SPSS Inc, Chicago, USA). Data was presented as median, mean ± SD, or percentage from the total number. Evaluation of the association between serum NT-proBNP levels and quantitative variables was carried out using Pearson's correlation coefficient. Serum levels of NT-proBNP were compared between passive smokers and controls using an independent *t*-test. The same test was used to assess the effect of sex on serum NT-proBNP.

Ethical considerations

The study design, method, and objectives were consistent with the world medical association declaration of Helsinki 2013. The study protocol was approved by the research ethical committee at El-Fayoum University. The protocol was discussed with all the study participants, and a written informed consent was obtained from each participant. All participants were volunteers and were referred to by numbers. At the end of the study, counseling of participants with high serum levels of NT-proBNP was performed.

Results

Characteristics of the study participants

A total of 80 participants were enrolled in the study: 60 passive smokers and 20 healthy matched controls. Their ages ranged from 20 to 35 years. The male to female ratio was 1 : 1. Table 1 summarizes the demographic, clinical, passive smoking, and serum NT-proBNP data of the study participants. All passive smokers were currently exposed to second-hand smoke of cigarettes, 55 (91.7%) were intimately related to the active smoker, and only five (8.3%) were occasionally passive smokers.

Effect of duration and extent of exposure to second-hand smoke on serum levels of NT-proBNP

The relationship between duration of passive smoking and extent of exposure to second-hand smoke, expressed as the pack per year history of passive smoking, was assessed. The results showed a significant and a highly significant positive correlation between serum NT-proBNP levels and both the duration and the amount of passive smoking, respectively, as shown in Table 2.

Other variables that could affect serum levels of N-terminal pro-B-type natriuretic peptide

The effect of quantitative variables such as age, body weight, and SBP on serum NT-proBNP was assessed in all the study participants. Results are shown in Table 3. It showed an insignificant positive correlation between

Table 1 Characteristics of passive smokers (*n* = 60) and the matched controls (*n* = 20)

Variables	Passive smokers (*n* = 60)	Controls (*n* = 20)
Demographic		
Age (mean ± SD)	28 ± 4.5	26.8 ± 3.3
Sex (male) [*n* (%)]	30 (50)	10 (50)
Residence [*n* (%)]		
Urban	47 (78.3)	19 (90)
Rural	13 (21.7)	2 (10)
Occupation [*n* (%)]		
Housewife	12 (20)	7 (35)
Employed	36 (60)	12 (60)
Student	10 (16.7)	1 (5)
Unemployed	2 (3.3)	0 (0)
Clinical		
Body weight (kg)	84.8 ± 11.6	81.6 ± 8.5
SBP (mm/Hg)	127.18 ± 9.22	120.7 ± 9.7
Independent *t*-test		
Difference between means	6.58 ± 2.41	—
P-value	0.007**	—
Passive smoking history		
Duration of passive smoking (years)	7.7 ± 1.9	—
Living with the active smoker		
Yes	55 (91.7)	—
No	5 (8.3)	—
Pack per year history of passive smoking	7.6 ± 4.0	—
Serum NT-proBNP (pg/ml)		
Mean ± SD	251.2 ± 46.9	148.3 ± 29.7
Median	259.5	147.0
Minimum	115	93
Maximum	341	189

Data were presented as mean ± SD, median, or as percentages from the total number as appropriate; The level of significance was set at 0.05; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

Table 2 Correlations between serum levels of N-terminal pro-B-type natriuretic peptide and the duration and amount of exposure to second-hand smoke

Variables	*r*	*P* value	Significant *P*
Duration of passive smoking	0.313a	0.015	0.05
Pack per year history of passive smoking	0.763b	0.0001	0.01

R, correlation coefficient; aCorrelations are significant at the 0.05 level; bCorrelations are significant at the 0.01 level.

Table 3 Correlations between N-terminal pro-B-type natriuretic peptide and quantitative variables of passive smokers and the matched controls

Variable	Passive smokers (*n* = 60)	Controls (*n* = 20)	All (*n* = 80)
Age (years) [*r* (*P*)]	0.100 (0.448)	0.211 (0.372)	0.158 (0.162)
Weight (kg) [*r* (*P*)]	0.381 (0.003)**	0.280 (0.231)	0.328 (0.003)**
SBP (mm/Hg) [*r* (*P*)]	0.894 (0.000)**	0.135 (0.571)	0.711 (0.000)**

NT-proBNP, N-terminal pro-B-type natriuretic peptide; *r*, correlation coefficient; SBP, systolic blood pressure; **Correlations are significant at the 0.01 level.

age and NT-proBNP in all the study participants. Also, the correlation between weight, SBP, and NT-proBNP in the controls was insignificant. However, a highly significant positive correlation was observed between weight, SBP, and NT-proBNP in passive smokers.

The effect of sex on serum levels of NT-proBNP was also assessed; the results obtained showed an insignificant difference between men and women for NT-proBNP ($P = 0.610$, the difference between means was -7.375 ± 14.41).

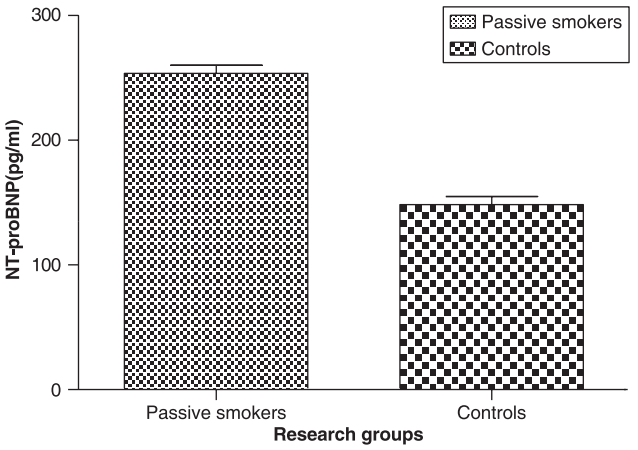
Serum NT-proBNP (pg/ml) levels in passive smokers and the control group

Serum levels of NT-proBNP (pg/ml) in passive smokers and controls were compared using an independent *t*-test. The results showed a highly significant difference between the means of the two groups ($P < 0.0001$); the difference between means was 105.4 ± 11.64 and Fig. 1 shows the distribution of NT-proBNP in passive smokers and controls. The ranges of serum levels of NT-proBNP in passive smokers and controls were expressed in percentages. Figure 2 shows a pie chart indicating that 15% of passive smokers had high NT-proBNP, and 42 and 43% had a high normal and normal NT-proBNP, respectively. However, serum NT-proBNP of the controls was 100% in the normal range.

Discussion

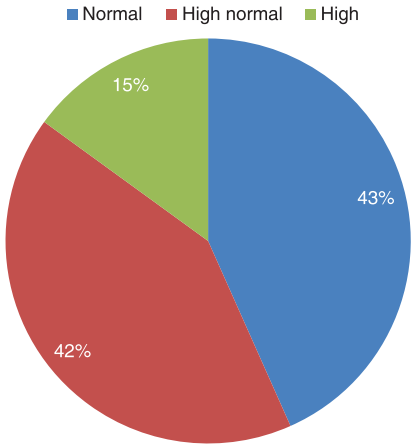
Smoking and exposure to second-hand smoke have been linked to a spectrum of cardiovascular and pulmonary disorders [10]. In 2011, Stamm *et al*. [11] found that elevated NT-proBNP is associated with mortality in tobacco smokers independent of airflow obstruction. In 2008, the European Society of Cardiology recommended the use of natriuretic peptides as a good negative biomarker of heart failure in primary care settings [12]. Accordingly, we assumed that NT-proBNP could be a valuable screening tool for Lv dysfunction in passive smokers. Thus, first, we carried out this study to evaluate the effect of passive smoking on serum levels of NT-proBNP. Our results showed significantly high serum levels of NT-proBNP in passive smokers compared with the control group. Also, our results showed a strong positive association between NT-proBNP and both the duration of exposure to second-hand smoke and the estimated pack per year history of passive smoking. These results, together with the results of Otsuka *et al*. [13], showed that passive smoking could increase serum NT-proBNP as much as active smoking. Otsuka *et al*. [13] examined the relation of smoking status to serum levels of NT-proBNP in middle-aged men without overt

Figure 1



Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) in passive smokers (n = 60) and the control group (n = 20). ***The difference between the two groups is highly significant (P < 0.0001).

Figure 2



Groups of passive smokers according to serum levels of N-terminal pro-B-type natriuretic peptide.

cardiovascular disease. They found that NT-proBNP levels were significantly higher among current smokers than never smokers [13].

Also, the current study investigated the association between serum NT-proBNP and other variables that could have an effect on Lv function such as sex, age, body weight, and SBP. The results obtained showed an insignificant effect of sex and age on serum NT-proBNP. These results are inconsistent with other researchers who found that NT-proBNP is higher in women and in older age groups [14,15] and also inconsistent with Hildebrandt *et al.* [16], who concluded that the use of age-dependent limits of NT-proBNP will increase the diagnostic accuracy and reduce missed diagnosis of Lv dysfunction, and rationalize echocardiographic follow-up. These conflicting results can be attributed to the fact that in this study, the participants' age range was relatively younger compared with those in other studies. At this age, symptoms and signs of ventricular dysfunction are rare [17].

An *in-vitro* study showed that BNP can stimulate human adipocytes to increase the production of adiponectin [18]. Adiponectin serum levels were found to be correlated negatively with body fat [19]. In this study, the effect of body weight on serum NT-proBNP was also analyzed and the results obtained showed a positive correlation between body weight and serum NT-proBNP; however, this was significant in passive smokers and insignificant in the control group. These results can be attributed to the small sample size of the control group. Also, these results are inconsistent with Wang *et al.* [20], who showed that the fasting NT-proBNP level was associated negatively with metabolic syndrome in elderly individuals, and that age, triglyceride, body fat mass, and height were independent predictors of fasting serum NT-proBNP levels. This could be explained by the older age of participants in their study, 65 years or older. Moreover, as aging is associated with various changes in body fat [21], the effect of body fat in NT-proBNP should be investigated in different age groups. However, our results were in contrast to others who showed a negative association between metabolic syndrome and NT-proBNP [22]. This could be explained by the fact that the current study investigated the relationship between only body weight and NT-proBNP compared with these studies in which many variables were analyzed such as serum triglycerides and body mass index. Meanwhile, our results were consistent with Peter *et al.* [23], who found that NT-proBNP levels are not lower in obese compared with nonobese diabetics.

In terms of the effect of SBP on serum NT-proBNP, the current study showed a significantly higher mean SBP among passive smokers compared with the healthy controls. Also, a significant positive association was observed between SBP and serum NT-proBNP. These results confirmed the results of other researchers who found that exposure to second-hand smoke increases both systolic and diastolic blood pressure [24]. Also, these results confirmed the findings of Seyedzadeh *et al.* [25], who investigated the effect of exposure to second-hand smoke on both systolic and diastolic blood pressures of elementary school children. They concluded that systolic and diastolic blood pressures were higher in the exposure group compared with the nonexposure group.

Conclusion

We have shown that serum NT-proBNP is significantly higher than normal in passive smokers without overt

cardiovascular or pulmonary disease. Accordingly, we recommended the use of serum NT-proBNP measurements to select passive smokers who are in need of further cardiovascular assessment tools such as echocardiography. However, there is still a need for further studies to investigate the relationship between various echocardiographic parameters and serum levels of NT-proBNP. We also recommend the development of a feasible, nonexpensive, and commercially available biochemical assay of NT-proBNP to monitor treatment response in various cardiovascular disorders.

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Conflicts of interest

There are no conflicts of interest.

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