

Cardiovascular Autonomic Function in Microalbuminuria

SUDHANVA .S, DHANANJAYA.J.R, YATHISH.T.R, MAMATHA.C.N

ABSTRACT

Background: Microalbuminuria (MA) has emerged as a risk factor for left ventricular hypertrophy, myocardial infarction, peripheral vascular diseases and retinopathy which is independent of blood pressure.

Aim: The present study was designed to investigate the relationship between cardiovascular autonomic function and microalbuminuria.

Methods: The study comprised of 200 male subjects of age group >50 years, who were classified into 2 groups of 100 subjects each. 1) Subjects with MA and 2) Age matched healthy controls without MA. The tests which were performed were 1) Heart rate response to deep breathing, Valsalva maneuver and standing. 2) Blood pressure response to standing and to a

sustained handgrip. Individual tests were given a score of 0, 1, or 2 and an overall autonomic test score of 0-10 was obtained.

Results: The mean autonomic score in the controls and in subjects with MA were 5.73 ± 1.26 and 7.00 ± 1.80 respectively. The coefficient of variation (CV%) of the controls and the subjects with MA was 21.9 and 25.7 respectively. A significant difference in the autonomic score was observed in the subjects with MA ($p < 0.01$) as compared to the controls.

Conclusion: The impairment of the autonomic function leads to an increased renal blood flow, glomerular hyperfiltration, and sodium excretion, which accelerates its progression to microalbuminuria. In conclusion, individuals with microalbuminuria should be diagnosed early to minimize cardiovascular complications.

Key Words: Cardiovascular autonomic function, Microalbuminuria, Cardiovascular tests

INTRODUCTION

Quantitative cardiovascular autonomic function tests are widely used to detect, verify and quantify the cardiovascular autonomic dysfunction. They have been tested for their validity and reliability. These tests are performed since their procedures are straightforward, reproducible and non-invasive.

Microalbuminuria, which is defined as the elevation of urinary albumin excretion in the range of 30 to 300 mg/24 h or 20-200 $\mu\text{g}/\text{min}$, is strongly associated with endothelial dysfunction, which increases the risk of nephropathy and cardiovascular complications, including atherosclerotic coronary disease, stroke, peripheral vascular disease and cardiovascular mortality. Earlier studies have suggested that patients with cardiovascular autonomic neuropathy had a higher prevalence of microalbuminuria than patients without cardiovascular autonomic neuropathy. So, the present study was aimed at evaluating the association of cardiovascular autonomic functions, as assessed by quantitative cardiovascular autonomic function tests with microalbuminuria in the age group above 50 years.

MATERIALS AND METHODS

This observational study was conducted in the Institute of Sri Devaraj URS Medical College, Kolar, Karnataka, India during March 2006 to March 2007. The study was conducted after obtaining informed consent from the study participants, and after taking clearance from the ethical committee of the institution. The study comprised of 200 male subjects of age group >50 years. The presence of microalbuminuria was detected by a colourimetric end point test by using the pyrogallol red reagent. Clean, mid-stream "spot" urine was collected, as this was convenient for the patient

than collecting a 24-hour urine specimen. None of the subjects were suffering from any acute and chronic cardiovascular and pulmonary diseases. None were on drugs which altered the renal function and the autonomic functions. They were classified into 2 groups of 100 subjects each.

1. Subjects with microalbuminuria.
2. Control group consisting of age matched healthy subjects without microalbuminuria.

The subjects were instructed not to consume coffee, tea or cola, 12 hours before the tests and were asked to have a light breakfast two hours before the tests. The subjects were asked to relax in the supine position for 30 minutes. The resting heart rate was recorded on a standard electrocardiograph (ECG) from lead II. The blood pressure (BP) was measured by using a sphygmomanometer. The cardiovascular tests which were performed are explained in detail below in their order of execution. These tests were demonstrated to the subjects.

PROCEDURE OF AUTONOMIC EVALUATION [2]

1. Deep Breathing Test: In the sitting position, the subject was asked to breathe quietly and deeply at the rate of 6 breaths per minute. A continuous ECG was recorded for six cycles. The maximum and minimum R-R intervals in lead II were measured during each breathing cycle and were converted to beats per minute. The result was then expressed as the mean of the difference between the maximum and the minimum heart rate for six measured cycles in beats/minute [1].

Deep Breathing Difference (DBD) = Mean of heart rate differences in 6 breath cycles.

2. Heart-Rate Variation to Valsalva Maneuver: The subject was seated comfortably and was asked to blow into a mouth-piece which was connected to a mercury sphygmomanometer, holding it at a pressure of 40 mm Hg for 15 seconds, while a continuous ECG in lead II was being recorded. The ECG was continued to be recorded for 30 seconds after the release of the pressure at the end of 15 seconds. The heart rate changes which were induced by the Valsalva maneuver were expressed as the ratio of the maximal tachycardia during the maneuver to the maximal bradycardia after the maneuver. This ratio was defined as the Valsalva ratio and was calculated as the ratio of the maximum R-R interval after the maneuver to the minimum R-R interval during the maneuver [1].

Valsalva Ratio (VR) = Maximal tachycardia/maximal bradycardia = Maximum R-R interval/minimum R-R interval.

3. Heart Rate Response to Standing (Postural Tachycardia Index): The subjects were asked to lie on the examination table quietly while the heart rate was being recorded on the ECG. They were then asked to stand-up unaided and the ECG was recorded for 1 minute. The shortest R-R interval at or around the 15th beat and the longest R-R interval at or around the 30th beat were measured [1]. The result was expressed as PTI = Longest R-R interval at the 30th beat/shortest R-R interval at the 15th beat.

4. Blood Pressure Response to Standing (Orthostatic Test): The subject was asked to rest in a supine position. The resting BP was recorded by using a sphygmomanometer. The subject was then asked to stand unaided and to remain standing unsupported for 3 minutes. The BP was recorded at 30 seconds and 3 minutes after standing up. The difference between the resting and the standing BP levels was calculated. The fall in systolic BP at 30 seconds on standing was noted [1].

5. Blood Pressure Response to Sustained Handgrip: The patient was asked to compress the inflated blood pressure cuff to the maximum possible extent with one hand and the reading on the manometer was noted. The patient was asked to maintain the pressure of the cuff in such a way as to keep the manometer reading at 30% of the maximum force for a period of 3 minutes. The maximum reading of the diastolic blood pressure was recorded during the procedure. Then, the rise in the diastolic blood pressure was calculated by subtracting the resting diastolic blood pressure from this value.

The interpretation of these tests was done according to the norm which was adopted by Ewing et al (1980) [2].

RESULTS

The results which were obtained by performing the individual cardiovascular tests were given a score of 0, 1, or 2 depending on whether they were normal, borderline or abnormal respectively. An overall autonomic test score of 0-10 could then be obtained. The

data which was so obtained was entered into a suitable master chart and was treated statistically.

Autonomic Score: The mean and SD of the autonomic score in the controls and in the subjects with MA were 5.73 ± 1.26 and 7.00 ± 1.80 respectively. The CV (%) of the controls and the subjects with MA was 21.9 and 25.7 respectively. There was a significant increase in the autonomic scores in the subjects with MA as compared to that of the controls. The autonomic scores of the subjects were significantly different from that of the controls ($p < 0.01$).

DISCUSSION

The observation of urinary protein as a sign of renal disease is one of the oldest examples in medical history, where individual measures are used as diagnostic markers. Until the 18th century, the uroscopist used his eyes, nose and sometimes taste to come to a diagnostic conclusion [3]. Renal function, glomerular filtration and tubular reabsorption and secretion have been described as the major mechanisms for urine formation, which can be used as a diagnostic mirror of pathological changes [3]. Microalbuminuria is associated with adverse health outcomes in adults [4].

Microalbuminuria is thought to be a consequence of an increased albumin leakage through the glomerular capillary wall as a result of increased permeability, an increased intraglomerular pressure or both. Recent evidence has pointed towards a more important and direct role of the endothelium in determining its permeability to albumin. In particular, the glycocalyx that fills the endothelial fenestrae, seems to be important for glomerular size and charge selectivity [5, 6]. Abnormalities in the endothelial glycocalyx may contribute to microalbuminuria but may also have been implicated in the pathogenesis of atherosclerosis. Thus providing a potential direct link between albuminuria and cardiovascular disease [7].

Microalbuminuria may precede the onset of non-insulin-dependent diabetes and is linked to aberrations in glucose and insulin metabolism even in the absence of diabetes. These research findings suggest that microalbuminuria may be an important risk marker in the general adult population [8].

The autonomic nervous system modulates the electrical and contractile activity of the myocardium via the interplay between the sympathetic and the parasympathetic activity [9]. An imbalance of autonomic control is implicated in the pathophysiology of arrhythmogenesis [9]. CAN results from damage to the autonomic nerve fibers of the heart, and the earliest indicator of CAN is a decrease in heart rate variation (HRV) during deep breathing. *Cardiovascular autonomic neuropathy* causes abnormalities in the heart rate control, as well as defects in the central and peripheral vascular dynamics. The clinical manifestations of CAN include exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension (OH), asymptomatic ischaemia, painless myocardial infarction (MI) and an increased risk of mortality [10]. Dysfunction of the vascular endothelium causes both microalbuminuria and

Heart Rate Response Tests (Parasympathetic Function)	Normal (score 0)	Borderline (score 1)	Abnormal (score 2)
Heart Rate Response to Valsalva Maneuver (VR)	1.21 or more	1.11-1.20	1.10 or less.
Heart Rate Response during Deep Breathing (DBD)	15 beats/min or more	11-14 beats/min	10beats/min or less.
Heart Rate Response to Standing (PTI)	1.04 or more	1.01-1.03	1.00 or less.
Blood Pressure (BP) Response Tests (Sympathetic Function)			
BP Response to Standing (fall in systolic BP)	10 mm Hg or less	11-29 mm Hg	30 mm Hg or more.
BP Response to Sustained Handgrip (rise in diastolic BP)	16 mm Hg or more	11-15 mm Hg	10 mm Hg or less.

[Table/Fig-1]: Cardiovascular autonomic function tests and autonomic score

Groups	Autonomic Score			Inference
	Mean	S.D.	CV (%)	
Control	5.73	1.26	21.9	F=112.63 p< 0.01
MA	7.00	1.80	25.7	

[Table/Fig-2]: Mean, Standard deviation (SD), Coefficient of variation (CV%) and one way ANOVA used to compare autonomic scores between the 2 study groups.

cardiovascular disease [11]. The endothelium is an important site of control of the vascular functions [12]. Endothelial dysfunction can be defined as any change in the endothelial properties that is inappropriate with regards to the preservation of organ function. Therefore, many types of endothelial dysfunction exist, depending on which function is affected (e.g., the regulation of haemostasis and fibrinolysis, vasomotor activity, permeability to macromolecules, leukocyte adhesion and vascular smooth muscle cell proliferation) [11]. The basement membrane synthesis may be altered, which can contribute to arterial stiffening and increased microvascular permeability the vascular tone and permeability may increase [13].

The findings of the present study were in conformity with those of earlier studies which were done by many researchers that are discussed below.

In 2004, Moran A et al performed the cardiovascular autonomic tests (Valsalva maneuver, the deep breathing test and the orthostatic test) on 132 patients with a mean age of 70 ± 5.6 years. The urine microalbumin-to-creatinine ratio was calculated. The blood pressure was measured at rest and by a 24-h ambulatory recording. They found that the urine microalbumin-to-creatinine ratio was higher in those with lower HRV. The resting and ambulatory blood pressure levels were negatively correlated with HRV and they were positively correlated with the urine microalbumin-to-creatinine ratio. They concluded that cardiovascular autonomic neuropathy and blood pressure were independently associated with microalbuminuria in older patients with type 2 diabetes [14].

In 1992, Klausen K et al, in the Third Copenhagen City Heart Study (1992 to 1994), on 2762 men and women who were 30 to 70 years of age, did a detailed cardiovascular investigation program, including a timed overnight urine sample. The participants were then followed up prospectively by using registers until 1999, with respect to coronary heart disease and until 2001 with respect to death. Urinary albumin excretion above the upper quartile, ie, $4.8 \mu\text{g}/\text{min}$ was associated with an increased risk of coronary heart disease and death, independent of age, sex, renal creatinine clearance, diabetes mellitus, hypertension, and plasma lipids. They concluded that microalbuminuria was a strong and independent determinant of coronary heart disease and death [15].

CONCLUSION

It was evident from the present study that significant cardiovascular autonomic neuropathy was present in subjects with microalbuminuria which has emerged as an important risk factor for left ventricular hypertrophy, myocardial infarction, stroke, peripheral vascular diseases and retinopathy which was independent of blood pressure. Hence, this study re-emphasizes the need for estimating the microalbuminuria levels for screening patients at early stages of cardiovascular diseases, in order to initiate steps to minimize disease progression as well as to prevent the complications that could arise at a later stage.

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AUTHOR(S):

1. Dr. Sudhanva S.
2. Dr. Dhananjaya J.R.
3. Dr. Yathish T.R.
4. Dr. Mamatha C.N.

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:

Department of Physiology, Hassan Institute of Medical Sciences, Hassan-573201, Karnataka, India.

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Sudhanva S.
Assistant Professor, Department of physiology
Hassan Institute of Medical Sciences
Hassan-573201, Karnataka, India
Mobile: +91-9480202815; E-mail: sudhanvadr@gmail.com

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