National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Evaluation of cardiovascular autonomic reactivity by cold pressor test in thyroid dysfunction in adults: A prospective case–control study

Sunita Milind Tiwale, Padmaja Rajey Desai

Department of Physiology, D. Y. Patil Medical College, Kolhapur, Maharashtra, India

Correspondence to: Sunita Milind Tiwale, E-mail: sunita.tiwale88@gmail.com

Received: November 16, 2016; **Accepted:** December 02, 2016

ABSTRACT

Background: Changes, in thyroid status, have pronounced effects on cardiovascular system reflecting autonomic dysfunction and increased morbidity. Exact interaction between autonomic nervous activity and thyroid hormones is controversial. **Aims and Objective:** The cold pressor test (CPT) was used to evaluate cardiac autonomic function in thyroid patients and compared with age and sex-matched healthy controls (18-45 years). **Materials and Methods:** This was a prospective case–control study. By clinical examination and serum levels of (T_3, T_4 and TSH) three groups hypothyroid, hyperthyroid and control group were categorized and blood pressure (BP) responses to CPT were evaluated in these groups. Statistical analysis was performed using student's *t*-test. **Results:** In hyperthyroid group, rise in systolic BP after CPT is not as that of control group. However, the difference in mean rise is statistically highly significant. While in hypothyroid group rise in diastolic BP is statistically highly significant as compared to that of control group. **Conclusion:** In hypothyroidism, lack of direct action of thyroid hormones is compensated by increased basal sympathetic tone which exhibits blunted sympatho - excitatory responses leading to aortic stiffness and resistance. This prevents fall in systolic pressure and further reduces vagal tone. Hence, rise in systolic BP after CPT declined but insignificant ($P > 0.05$). In hyperthyroidism, significant decrease ($P < 0.01$) in the rise in systolic BP after CPT suggests reduced parasympathetic and sympathetic activity. In hypothyroidism, a significant rise in diastolic BP after CPT ($P < 0.01$) suggests impaired response to beta receptors, over activity of alpha receptors and endothelial dysfunction resulting in increased peripheral resistance. In hyperthyroidism, insignificant rise ($P > 0.05$) in diastolic BP after CPT suggests direct action of thyroid hormone on vascular smooth muscles causing vasodilatation and reduced vagal tone decreasing sympathetic activity. Thus, the study revealed thyroid dysfunction leads to sympathovagal imbalance affecting cardiac autonomic function.

KEY WORDS: Autonomic Function; Hypothyroidism; Hyperthyroidism; Cold Pressor Test

INTRODUCTION

Thyroid hormone acts on almost every organ and system of the body. Changes, in thyroid status, are associated with changes not only in cardiac and vascular functions but also in autonomic regulation of cardiovascular (CV) system.[1,2] On reviewing the literature, a great deal of uncertainty persists regarding the exact interaction between autonomic functions and thyroid hormones in controlling the various organ systems.[3] The clinical picture of hyperthyroidism suggests increase in sympathetic activity but the plasma norepinephrine levels are normal or decreased.[4] Hypothyroidism shows reduced sympathetic activity.[1] However, the plasma norepinephrine levels are increased.[4]

Temperature and other environmental stressors are known to affect heart rate (HR) and blood pressure (BP). Sudden and increasingly painful cold stress causes massive discharge of

Access this article online

Website: www.njppp.com

DOI: 10.5455/njppp.2017.7.1132402122016

Quick Response code

the sympathetic nervous system and release of norepinephrine. This sympathetic discharge triggers responses in the CV system that includes arteriolar constriction, increased HR and increased cardiac contractility. These responses combine to increase BP (known as the pressor response),[5] and testing a subject with cold stress in this fashion is known as the cold pressor test (CPT). The CPT has been used clinically to evaluate cardiac autonomic function[6] and as an experimental pain stimulus[7] as an index for screening subjects for hypertension.[8,9] The CV response to the CPT can predict the future development of hypertension. Studies have indicated that persons who are at increased risk for developing early hypertension, show stronger vascular reactions to the CPT than others.[10] CPT as a standard stimulus to study the vasomotor response was introduced in 1932 (Hines and Brown, 1936). The subjects who showed greater response in his study were called hyper-reactors. Some of these hyper-reactors may possibly be candidates for hypertension in future.[11,12] This motivated us to undertake the present study. In the study, we have evaluated the cardiac autonomic status by assessing the effect of CPT to BP responses in adult hyperthyroid and hypothyroid patients. This will serve as an important step in the management of thyroid disease. Studies have suggested that very good metabolic control can achieve reversal of autonomic abnormalities decreasing the morbidity of thyroid patients.[13,14]

Objectives

1. Primary objective: To evaluate the cardiac autonomic status in adult hyperthyroid and hypothyroid patients by CPT.
2. Secondary objective: To study the correlation between thyroid status and the autonomic functions regulating CV system.

MATERIALS AND METHODS

The present quantitative, prospective, and comparative case–control study was conducted in the department of Physiology, in D. Y. Patil Medical College, Kolhapur, during the period of May 2015 to August 2016. This study was approved by the institutional ethical committee. After the ethical committee clearance, clinically diagnosed and untreated 30 hyperthyroid and 30 hypothyroid patients of age group 18 to 45 years were assessed and compared with age and sex-matched 30 healthy controls. The prevalence of thyroid disease was found to be high in females than males, hence each group comprised of 25 females and five males.[15] The effect of CPT on BP responses was studied to evaluate cardiac autonomic functions. Patients suffering from others conditions known to affect autonomic functions were excluded from the study, e.g., diabetes mellitus, coronary heart disease, electrolyte imbalance, leprosy, anemia, and pregnancy.

All the patients and controls were taken from Dr. Milind Patwardhan's Endocrine Research Center, Miraj. Based on general history, clinical examination and hormonal assays of T_3, T_4 and TSH, they were categorized as hyperthyroid, hypothyroid and Normal/Control group. Permission was taken from the Head of the center. Informed consent for experimentation was obtained from all patients and healthy controls. All subjects were tested under similar laboratory conditions. The subjects were allowed an hour to get familiarized with experimental and environmental conditions. The nature of the CPT was explained to subjects beforehand to allay their apprehension. Laboratory thermometer was used to record the temperature of ice-cold water so as to maintain the temperature at 4°C in CPT.

Procedure: CPT: Subject was asked to take rest in supine position for 15 min.

Then in sitting position, subject's BP was recorded by sphygmomanometer with 12 cm cuff width first by palpatory and then by auscultatory method. Then, subject was asked to place one hand in freezing 4°C water for 1 min. At the end of it, systolic and diastolic BP was measured from the other arm before removing the hand from cold water. Normally, there is increase in systolic BP by 10-20 mm of Hg and diastolic BP by 0-10 mm of Hg.[12]

Statistical analysis is performed using SPSS version 23. Numerical data are expressed as Mean ± S.D. Quantitative data, i.e., the difference in systolic and diastolic BP s before and after CPT between the study groups (Thyroid patients, i.e., hypothyroid and hyperthyroid with healthy age and sex matched controls) was evaluated using unpaired student's *t*-test. $P < 0.05$ was considered statistically significant.

RESULT

The mean values of difference (mean rise) in systolic BP after CPT in hypothyroid is decreased as compared to control group. However, this difference in mean rise is statistically insignificant (Table 1, Graph 1). The mean value of the difference (mean rise) in systolic BP after CPT in hyperthyroid group is declined as compared to control group. This difference in mean rise is statistically highly significant (Table 1, Graph 1).

The mean value of the difference (mean rise) in diastolic BP after CPT in hypothyroids is increased. This difference in mean rise is statistically highly significant (Table 2, Graph 2). The mean value of difference (mean rise) in diastolic BP after CPT in hyperthyroids is declined. This difference in mean rise is statistically insignificant (Table 2, Graph 2).

DISCUSSION

In this study, CPT was performed to evaluate cardiac autonomic function and assess the integrity of the

Table 1: Comparison of rise of systolic BP. (mm of Hg) after cold pressor test between hypothyroid, control and hyperthyroid groups

Systolic blood pressure

Status	Mean+SD			Diff in mean rise	*t*	*P*	Significance
	Before test	After test	Rise in systolic BP				
Hypothyroid	123.8±18.68	138.6±16.4	14.8±14.49	3.66	1.03	*P*>0.05	Nonsignificant
Control group	126.66±16.02	145.13±17.07	18.46±12.95	8.46	2.85	*P*<0.01	Highly significant
Hyperthyroid	134.4±16.23	144.4±19.09	10±9.79				

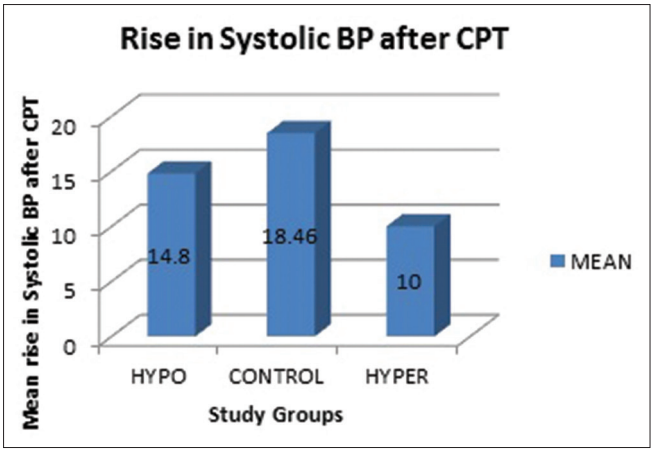
SD: Standard deviation, BP: Blood pressure

Table 2: Comparison of rise of diastolic BP. (mm of Hg) before and after cold pressor test between hypothyroid, control and hyperthyroid groups

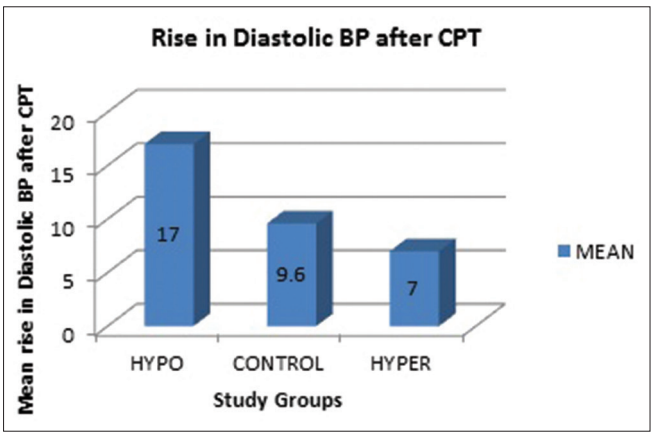
Diastolic blood pressure

Status	Mean+SD			Diff in mean rise	*t*	*P*	Significance
	Before test	After test	Rise in diastolic BP				
Hypothyroid	83.27±10.63	100.26±12.5	17±11.81	7.4	2.92	*P*<0.01	Highly significant
Control group	80.67±8.23	90.26±8.9	9.6±7.24	2.6	1.15	*P*>0.05	Insignificant
Hyperthyroid	83.8±10	90.8±11.34	7±9.97				

BP: Blood pressure, SD: Standard deviation



Graph 1: Rise in Systolic BP after CPT



Graph 2: Rise in Diastolic BP after CPT

sympathetic and parasympathetic system in thyroid patients and compared with healthy subjects. In hypothyroid patients, the mean value of difference (mean rise) in systolic BP after CPT decreased but statistically insignificant $P > 0.05$ (95% confidence interval: ± 5.19, Range: 9.61-19.99) as compared to control group (Table 1 and Graph 1). These findings are similar to the studies done by Foley and Hasser,[1] Klein and Ojamaa,[13] and Fazio et al.[14]

They suggest that thyroid status alters the balance of sympathetic to parasympathetic tone in the heart. Hypothyroidism alters the relative contribution of systems that maintain resting BP and HR with predominant sympathetic influence at rest. There is increased basal sympathetic tone to compensate for thyroid hormone deficiency, and this reduces reflex activation of sympathetic system during stress and exercise. As noted by some investigators, it further results in hypofunctioning of parasympathetic tone.[16,17] Some investigators expressed their views that hypothyroidism alters the responsiveness to sympathetic stimulation by modulating adrenergic receptor functions. There is decreased response to beta-adrenergic stimulation leading to aortic stiffness (impaired elastic properties of aorta) resulting in aortic resistance which further prevents fall in systolic BP. Furthermore, number of beta-adrenergic receptors is decreased.[18]

Few studies suggest that there is a decrease in the direct chronotropic and ionotropic effect of thyroid hormone on SA node and myocardium by significant reductions in the transcription of pacemaker channels and decrease in vagal activity in hypothyroids compared to control group.[14,16,19] So no much increase in HR, no increase in force of contraction. Hence, cardiac output and systolic BP is not much enhanced (blunted systolic BP response in hypothyroid) than that in control group.

The mean value of the difference (mean rise) in systolic BP after CPT in hyperthyroid group is declined as compared to control group. However, this difference in mean rise is statistically highly significant $P < 0.01$ (95% confidence interval: ± 3.5, Range: 6.5-13.5 (Table 1 and Graph 2). These findings are in accordance with Foley and Hasser[1] The probable reason suggested is increased T_3 and T_4 leads to unbalanced sympathovagal tone, i.e., decreased vagal tone and normal or reduced sympathetic tone.[2,3] Few investigators expressed the view that the effects of thyroxin and catecholamines are additive.[20] Our study is similar to that done by Shuvy et al. in hyperthyroid subjects.[21]

Few studies report that systolic BP is increased in 1/3rd of hyperthyroid patients which is due to the inability of the vascular system to accommodate the increase in stroke volume.[19,20] Our study is similar to that of Biondi et al.[22] which reports that in hyperthyroidism compliance of the arterial tree is decreased due to increase in the rate of contraction. The metabolic rate of the body is increased. To fulfill these increased metabolic demands, certain adaptive changes occur in the CV system. Effects of thyroid hormone on peripheral circulation play a central role in regulating CV performance. By reducing systemic vascular resistance, thyroid hormones shift blood from arterial tree to venous compartment, increasing venous return to the heart.

At the same time by increased HR and improving ventricular diastolic function, (increased transmitral protodiastolic pressure gradient, i.e., increased atrial pressure) and shortening of left ventricular isovolumetric relaxation time there is early mitral valve opening and early left ventricular filling by enhanced ventricular suction. This allows the increased venous return to be accommodated without relevant changes in left ventricular end diastolic volume (either it is increased or may remain constant).

Thus, there is synergistic interaction between increased HR and ventricular preload. So cardiac output is increased or may remain constant, similarly the systolic BP is increased or may remain constant in hyperthyroidism.

The increased HR reduces the dynamic compliance of the arterial tree and increases the aortic input impedance which in turn increases systolic BP. The increase in systolic BP counteracts the marked reduction in diastolic BP and thus maintains mean arterial pressure and increases the pulse pressure. In addition, T_4 modulates rate of transcription of multiple genes which increases synthesis of transport proteins.[11,23]

The rise in diastolic B.P after CPT in hypothyroid group is statistically highly significant $P < 0.01$ (95% confidence interval: ± 4.23, Range: 12.77-21.23) as compared to that of control group (Table 2 and Graph 2). These findings are similar to those of Matsukawa et al. and J. Burggraff et al. In hypothyroidism, the muscle sympathetic nerve reactivity is exaggerated leading to increased systemic vasculature resistance (SVR). There is altered response to β receptors and over activity of α receptors. Furthermore, Noradrenaline secreted at nerve terminals has potent action on α receptors.[24,25] Few studies have suggested that nitric oxide (NO) is involved in controlling the regulation of vascular tone. During CPT increased shear stress stimulates endothelial cells to release NO which mediates relaxation of microcirculatory smooth cells and increases perfusion. Thyroid dysfunction can alter capacities for the formation and response to NO.[26] Even the mild form of thyroid hormone deficiency impairs vascular function by damaging endothelial function at the level of the peripheral vasculature.[27-30] This is associated with increased vascular smooth muscle tone, arterial stiffening and intima - media thickness. T3 rapidly stimulates phosphatidylinositol 3 - kinase/Akt signaling and increases nitric acid synthase activity "nitric oxide synthase" in endothelial cells by a receptor - mediated nongenomic action and thus induces vasodilatation.[31-33] So in hypothyroid, patients response to CPT leads to severe vasoconstriction. This results in marked increase in diastolic pressure.

In our study, the magnitude of rise in diastolic B.P. after CPT in hyperthyroid group is declined but statistically not significant $P > 0.05$ (95% confidence interval: ± 3.57, Range: 3.43-10.57) (Table 2 and Graph 2). These findings are similar to those of Foley and Hasser[1,25] which suggests that in hyperthyroidism the sympathetic activity is normal or reduced. Excess of thyroid hormone leads to vasodilatation due to direct action of T_3 on vascular smooth muscles leading to relaxation. Another mechanism is due to excessive endothelial NO production, vascular reactivity is exaggerated because of enhanced sensitivity of the endothelial component. Hence, the rise in diastolic BP is same as that seen in normal subjects.

Hypothyroidism or hyperthyroidism account for some of the change in autonomic outflow at rest and for altered regulation of autonomic functions in response to various stresses.[34] Our study shows similar findings to that of Mahajan et al., where they have found primarily sympathetic function abnormality along with selective parasympathetic dysfunction in hypothyroid patients.[35] Other studies have demonstrated that endothelial dysfunction of the peripheral vasculature is reversible in subclinical hypothyroid patients after replacement therapy with L thyroxine. L thyroxine restored NO availability thereby resulting in TSH normalization.[18,36,37]

A potential limitation of our study is that we did not measure HR during the CPT, which has shown good reproducibility in short-term test studies.

Other studies have shown that timely treatment can achieve reversal of autonomic abnormalities, decreasing the morbidity of thyroid patients.[12,14,17-20,25,29]

Further studies: To evaluate reversal of autonomic abnormalities in thyroid patients taking treatment and have achieved euthyroid status by autonomic function tests.

CONCLUSION

From the result of this study, it can be concluded that thyroid dysfunction leads to sympathovagal imbalance leading to cardiac autonomic disturbance. In hypothyroidism, lack of direct action of thyroid hormones is compensated by increased basal sympathetic tone. This exhibits blunted sympathoexcitatory responses further reducing vagal tone. There is altered responsiveness to sympathetic stimulation, i.e., impaired response and decrease in the number to beta receptors. However, the impaired response leads to aortic stiffness (impaired elastic properties) resulting in aortic resistance, which further prevents fall in systolic pressure. Hyperthyroidism leads to low excitability of cardiac vagal motor neurons, reducing parasympathetic activity. At the same time, direct action of thyroid hormone on SA node and myocardium has additive effect to sympathetic system resulting in hyperadrenergic state. But in the presence of reduced vagal tone, the sympathetic activity appears to be enhanced, though it is normal or reduced.

In hypothyroidism, there is impaired response to beta receptors leading to over activity of alpha receptors and increase sympathetic activity in the smooth muscles of vessels, resulting in increased systemic vascular resistance. In addition increased left ventricular end-systolic volume also contributes to rise in diastolic BP. In hyperthyroidism, excess of thyroid hormone has direct action on vascular smooth muscles leading to vasodilatation. Furthermore, the reduced vagal tone leads to decreased sympathetic activity. Thus, evaluation of the effect of thyroid state on CV system will serve as an important step in the management of thyroid disease. CPT, one of the non-invasive autonomic function tests will be useful in early detection of autonomic abnormalities. Timely treatment can achieve reversal of autonomic abnormalities, decreasing the morbidity of thyroid patients.

ACKNOWLEDGMENTS

We owe sincere thanks to Dr. Milind Patwardhan and Dr. Mrs. Patwardhan for providing us the patients and hormonal assay reports. We also acknowledge the faith and cooperation extended by all the patients.

REFERENCES

1. Foley M, Hasser EM. Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. Am J Physiol Heart Circ Physiol. 2001;280(5):H2061-8.
2. Levey GS, Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. Am J Med. 1990;88:642-8.
3. Kollai B, Kollai M. Reduced cardiac vagal excitability in hyperthyroidism. Brain Res Bull. 1988;20(6):785-90.
4. Coulombe P, Dussault JH, Walker P. Plasma catecholamine concentrations in hyperthyroidism and hypothyroidism. Metabolism. 1976;25(9):973-9.
5. Velasco M, Gómez J, Blanco M, Rodriguez I. The cold pressor test: Pharmacological and therapeutic aspects. Am J Ther. 1997;4(1):34-8.
6. Wirch JL, Wolfe LA, Weissgerber TL, Davies GA. Cold pressor test protocol to evaluate cardiac autonomic function. Appl Physiol Nutr Metab. 2006;31(3):235-43.
7. von Baeyer CL, Piira T, Chambers CT, Trapanotto M, Zeltzer LK. Guidelines for the cold pressor task as an experimental pain stimulus for use with children. J Pain. 2005;6(4):218-27.
8. Hines EA, Brown GE. The cold pressor test for measuring the reactivity of the blood pressure: Data concerning 571 normal and hypertensive subjects. Am Heart J. 1936;11:1-9.
9. Reiser MF, Ferris EB Jr. The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension. J Clin Invest. 1948;27(1):156-63.
10. Kelsey RM, Patterson SM, Barnard M, Alpert BS. Consistency of hemodynamic responses to cold stress in adolescents. Hypertension. 2000;36(6):1013-7.
11. Flaa A, Eide IK, Kjeldsen SE, Morten R. Sympathoadrenal stress reactivity is a predictor of future blood pressure: An 18-year follow-up study. Hypertens J Am Heart Assoc. 2008;52:336-41.
12. Jaju DS, Dixit MB, Purandare VR, Raje S. Heart rate and blood pressure responses of left handers and right handers to autonomic stressors. Indian J Physiol Pharmacol. 2004;48:31-4.
13. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001;344(7):501-9.
14. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res. 2004;59:31-50.
15. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. Indian J Endocrinol Metab. 2011;15 Suppl 2:S78-81.
16. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation. 1993;87(5):1435-41.
17. Karthik S, Pal GK, Nanda N, Hamide A, Bobby Z, Amudharaj D, et al. Sympathovagal imbalance in thyroid dysfunction in females: Correlation with thyroid profile, heart rate and blood pressure. Indian J Physiol Pharmacol. 2009;53(3):243-52.
18. Dernellis J, Panaretou M. Effects of thyroid replacement therapy on arterial blood pressure in patients with hypertension and hypothyroidism. Am Heart J. 2002;143(4):718-24.
19. Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007;116(15):1725-35.
20. Pietras RJ, Real MA, Poticha GS, Bronsky D, Waldstein SS. Cardiovascular response in hyperthyroidism. The influence of adrenergic-receptor blockade. Arch Intern Med. 1972;129(3):426-9.
21. Shuvy M, Arbelle JE, Grosbard A, Katz A. A simple test of one minute heart rate variability during deep breathing for evaluation of sympatovagal imbalance in hyperthyroidism. Isr

Med Assoc J. 2008;10(8-9):603-6.
22. Biondi B, Palmiers EA, Lombardi G, Fazio S. Effects of thyroid hormone on cardiac function. J Clin Endocrinol Metab. 2002;87(3):968-74.
23. Le Bouter S, Demolombe S, Chambellan A, Bellocq C, Aimond F, Toumaniantz G, et al. Microarray analysis reveals complex remodeling of cardiac ion channel expression with altered thyroid status: Relation to cellular and integrated electrophysiology. Circ Res. 2003;92(2):234-42.
24. Matsukawa T, Mano T, Gotoh E, Minamisawa K, Ishii M. Altered muscle sympathetic nerve activity in hyperthyroidism and hypothyroidism. J Auton Nerv Syst. 1993;42(2):171-5.
25. Burggraaf J, Tulen JH, Lalezari S, Schoemaker RC, De Meyer PH, Meinders AE, et al. Sympathovagal imbalance in hyperthyroidism. Am J Physiol Endocrinol Metab. 2001;281(1):E190-5.
26. McAllister RM, Albarracin I, Price EM, Smith TK, Turk JR, Wyatt KD. Thyroid status and nitric oxide in rat arterial vessels. J Endocrinol. 2005;185(1):111-9.
27. Biondi B, Galderrist M, Pagano L, Sidiropulos M, Pulcrano M, D' Errico A, et al. Endothelial - mediated coronary flow reserve in patients with mild thyroid hormone deficiency. Eur J Endocrinol. 2009;161:323-9.
28. Lekakis J1, Papamichael C, Alevizaki M, Piperingos G, Marafelia P, Mantzos J, et al. Flow mediated endothelium dependant vasodilatation is impaired in subjects with hypothyroidism, borderline hypothyroidism and high normal serum TSH levels. Thyroid. 1997;7(3):411-4.
29. Napoli R, Biondi B, Guardasole V, Matarazzo M, Pardo F, Angelini V, et al. Impact of hyperthyroidism and its correction on vascular reactivity in humans. Circulation. 2001;104(25):3076-80.
30. McAllister RM, Albarracin I, Jasperse JL, Price EM. Thyroid status and endothelium-dependent vasodilation in skeletal muscle. Am J Physiol Regul Integr Comp Physiol. 2005;288(1):R284-91.
31. Cikim AS, Oflaz H, Ozbey N, Cikim K, Umman S, Meric M, et al. Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. Thyroid. 2004;14(8):605-9.
32. Hiroi Y, Kim HH, Ying H, Furuya F, Huang Z, Simoncini T, et al. Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci U S A. 2006;103(38):14104-9.
33. Ojamaa K, Klemperer JD, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. Thyroid. 1996;6(5):505-12.
34. Bhatt AN, Kalsotra L, Yograj S. Autonomic reactivity with altered thyroid status. J K Sci. 2007;9(2):70-4.
35. Mahajan A, Lal R, Dhanwal DK, Jain AK, Chaudhari V. Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. Indian J Endocrinol Metab. 2013;17(3):462-4.
36. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Jolanta U. Weaver The beneficial effect of L – Thyroxine on cardiovascular risk factors, endothelial function and quality of life in clinical hypothyroidism: Randomized, crossover trial. J Clin Endocrinol Metab. 2007;92:1715-23.
37. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: Evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab. 2002;87(5):1996-2000.

How to cite this article: Tiwale SM, Desai PR. Evaluation of cardiovascular autonomic reactivity by cold pressor test in thyroid dysfunction in adults: A prospective case-control study. Natl J Physiol Pharm Pharmacol 2017;7(4):375-380.

Source of Support: Nil, **Conflict of Interest:** None declared.