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Pathophysiology of Neurally Mediated Syncope: Role of Cardiac Output and Total Peripheral Resistance

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Abstract

Syncope is a common clinical condition occurring even in otherwise healthy people without underlying cardiovascular disease. Neurally mediated syncope is by far the the most common cause of syncope in individuals without any structural heart disease. Based on traditional wisdom, loss of sympathetic tone with relaxation of vascular smooth muscle is the key mechanism underlying the pathophysiology of syncope, especially in patients without an acute decrease in heart rate. However, this concept has recently been challenged. Some microneurographic studies indicate that sympathetic withdrawal may not always be a prerequisite even for the development of classic “vasodepressor” forms of syncope. Conversely, a decrease in cardiac output appears to be a determinant factor for syncope in most circumstances. This article reviews the relative contribution of cardiac output versus sympathetic vasoconstriction in neurally mediated syncope in otherwise healthy individuals. It is suggested that a moderate to severe fall in cardiac output with or without vasodilatation may contribute to syncope.

Keywords

vasovagal syncope; the autonomic nervous system; stroke volume; heart rate; sympathetic activity; hemodynamics

Introduction

Over 1 million people in the United States (Soteriades *et al.*, 2002; Malasana *et al.*, 2011), many of whom are young women (Robertson, 1999), suffer from syncope each year. Neurally mediated (reflex) syncope is by far the most common cause of syncope in people without structural heart disease, but the exact mechanisms for these neural pathways and

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Disclosures
None.

their variations among individuals remain unclear. Many drugs have been tested in the treatment of recurrent syncope, for the most part with disappointing outcomes (Moya *et al.*, 2009). One major reason for the management challenge may be the complexity of the hemodynamic characteristics of syncope.

Based on the Sharpey-Schafer model (Sharpey-Schafer, 1956), syncope is produced by acute systemic vasodilatation, which may be elicited by forceful contractions of an empty left ventricle, the so called “empty heart syndrome”. Profound vasodilatation in the forearm has indeed been observed during syncope (Barcroft *et al.*, 1944; Barcroft & Edholm, 1945; Epstein *et al.*, 1968; Halliwill *et al.*, 1996; Dietz *et al.*, 1997a; Dietz *et al.*, 1997b). It has been thought that loss of sympathetic tone (Wallin & Sundlof, 1982; Morillo *et al.*, 1997; Mosqueda-Garcia *et al.*, 1997) leading to relaxation of vascular smooth muscle (Barcroft *et al.*, 1944; Barcroft & Edholm, 1945; Sharpey-Schafer, 1956; Epstein *et al.*, 1968) contributes importantly to neurally mediated syncope. However, this traditional concept has recently been challenged.

The new concept is that mechanisms other than sympathetic neural control may be responsible for the initiation and occurrence of syncope. This notion seems to be supported by several microneurographic studies showing that withdrawal of sympathetic activity is not always a prerequisite for (pre)syncope despite significant decreases of arterial pressure (Cooke *et al.*, 2009; Vaddadi *et al.*, 2010; Fu *et al.*, 2012).

Neurally mediated syncope is traditionally defined by three subtypes; vasodepressor, cardioinhibitory, and mixed type (Moya *et al.*, 2009). Recently, we have identified more precise characteristics of syncope based on the contribution of cardiac output and sympathetic vasoconstriction to hypotension (Fu *et al.*, 2012). Our data show that a moderate fall in cardiac output with coincident vasodilatation occurs in the majority (64%) of presyncopal individuals, while a severe fall in cardiac output, driven predominantly by a decrease in heart rate with no changes in total peripheral resistance at presyncope occurs in a smaller (36%) subset.

Contribution of cardiac output to syncope

Results from several laboratories suggest that cardiac output may be a key factor for syncope in humans. For example, Jardine *et al* reported, for the first time, that a progressive decrease in cardiac output may contribute to hypotension some minutes before syncope occurs (Jardine *et al.*, 2002). This work was furthered by studies showing that sublingual nitroglycerin may facilitate syncope by reducing cardiac output without evidence of sympathetic inhibition (Gisolf *et al.*, 2004). Subsequent research showed that circulatory patterns precipitating presyncope were not different between patients who used versus who did not use sublingual nitroglycerin (Verheyden *et al.*, 2008). In both groups marked hypotension was cardiac output-mediated, suggesting the underlying mechanism may be independent of the use of nitroglycerin (Verheyden *et al.*, 2008). Recently, we observed that all presyncopal individuals had a moderate to severe fall in cardiac output 1-2 minutes prior to syncope (Fu *et al.*, 2012). The fall in cardiac output can be driven by a decrease in heart rate (bradycardia) and/or a decrease in stroke volume.

Profound bradycardia or asystole of course will lead to a marked reduction in cardiac output. This notion was supported by our findings showing that the severe fall in cardiac output prior to syncope was driven predominantly by the decrease of heart rate (Fu *et al.*, 2012). However, previous atropine and cardiac pacing studies have yielded conflicting results, indicating that bradycardia may not always be the only factor in restricting cardiac output (Weissler *et al.*, 1957; Fujimura *et al.*, 1989; Sra *et al.*, 1993; Connolly *et al.*, 1999; Sutton *et al.*, 2000; Ammirati *et al.*, 2001; Connolly *et al.*, 2003; Raviele *et al.*, 2004). The timing of atropine injection may be critical; once presyncope begins, it is probably too late to stop it. Conversely, it is important to select patients who are good candidates for cardiac pacing. The International Study on Syncope of Unknown Etiology (ISSUE) 2 study hypothesized that spontaneous asystole should form the basis for patient selection for pacemaker therapy (Brignole *et al.*, 2006). Indeed, the recently published double-blind, randomized placebo-controlled ISSUE 3 trial has shown that permanent pacing is effective in reducing recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope (Sutton *et al.*, 2014). These results further support the notion that profound bradycardia or asystole plays a crucial role in the fall of cardiac output and the occurrence of syncope.

Many investigations have found that stroke volume decreases progressively and then rapidly at syncope (Jardine *et al.*, 2002; Kozlowski *et al.*, 2003; Verheyden *et al.*, 2007; Verheyden *et al.*, 2008; Folino *et al.*, 2010a; Fu *et al.*, 2012). Excessive blood pooling in the lower body and reduced venous return are responsible for the decrease in stroke volume during orthostasis. It was found that in patients with unexplained recurrent syncope, calf volume changes did not correlate to a symptomatic outcome during upright tilt (Bellard *et al.*, 2003). In addition, graded calf compression stockings failed to improve orthostatic tolerance in healthy individuals (Protheroe *et al.*, 2011). These findings suggest that blood pooling in the splanchnic and/or renal vascular bed(s) rather than the calf may contribute more importantly to syncope (Stewart *et al.*, 2004; Jardine, 2013). However, we cannot exclude the possibility that more blood may be pooled above the calf during orthostasis. The rapid decrease in stroke volume at syncope may be attributed to a reduction of cardiac contractility (Folino *et al.*, 2010b) or acute (rapid) venodilatation (Manyari *et al.*, 1996; Thomson *et al.*, 1996). An earlier study showed that venoconstriction rather than venodilatation occurred in the forearm or hand veins during syncope (Epstein *et al.*, 1968). It has been suggested that active venoconstriction in the limbs is not important to mild orthostatic response (Stewart *et al.*, 2001). Perhaps the problem is still rapid arteriolar vasodilatation, leading to redistribution of cardiac output even without venodilation at the onset of syncope.

Role of sympathetic activity and total peripheral resistance in syncope

Recent studies indicate that withdrawal of sympathetic activity may not directly contribute to syncope (Cooke *et al.*, 2009; Vaddadi *et al.*, 2010; Fu *et al.*, 2012). For example, it was found that sympathetic withdrawal occurred rapidly at presyncope, much later than the initial decrease in blood pressure (Cooke *et al.*, 2009; Fu *et al.*, 2012; Schwartz *et al.*, 2013). Persistence of muscle sympathetic nerve activity (MSNA) was reported during syncope in some people (Vaddadi *et al.*, 2010). We have also observed that in some individuals (all young females) sympathetic withdrawal does not occur during presyncope, and these individuals have a profound increase in plasma epinephrine concentration at presyncope

compared with those who show sympathetic withdrawal. These results raise the possibility that activation of the β_2-adrenergic receptor without sympathetic inhibition may also contribute to syncope. Indeed, Hart *et al* have demonstrated that the β-adrenergic receptors offset α-adrenergic vasoconstriction in young women but not young men or postmenopausal women (Hart *et al.*, 2011). Whether β_2-adrenergically mediated syncope occurs exclusively in young women needs to be investigated.

It is important to note that MSNA recordings are inherently limited to the skeletal muscle vasculature. However, animal studies showed that under most physiological conditions MSNA correlates and coheres approximately with renal and cardiac sympathetic nerve activities (Kamiya *et al.*, 2006). Whether sympathetic withdrawal in other vascular beds follows the same pattern as that in the skeletal muscle during syncope in humans remains unknown. It is also important to note that MSNA analyzed using the conventional methods may not reflect actual changes in sympathetic activity since it is an integrated signal. Analyzing nerve signal before integration, such as raw action potential, firing properties, and sympathetic neural recruitment patterns (Salmanpour *et al.*, 2008; Salmanpour *et al.*, 2011) may provide more insight into the role of sympathetic neural control in syncope.

We found that in the majority of presyncopal individuals, total peripheral resistance decreases earlier than the obvious reduction of MSNA (Fu *et al.*, 2012). However, we cannot exclude the possibility that vasodilatation in other vascular beds, such as splanchnic and renal circulations, could occur early in the development of syncope. It also is possible that the transduction of sympathetic outflow into peripheral vascular resistance may be altered before sympathetic withdrawal actually occurs (Iwase *et al.*, 2002; Kamiya *et al.*, 2005; Cooke *et al.*, 2009). Additionally, there may be a mismatch between nerve firing and norepinephrine release (Vaddadi *et al.*, 2011). Finally, β_2-adrenergic receptor mediated and/or humorally mediated active vasodilatation may contribute to the early decrease in total peripheral resistance (Dietz *et al.*, 1997b; Goldstein *et al.*, 2003). In our study, those with a prominent fall in cardiac output due to a fall in heart rate (all young females), total peripheral resistance remained stable prior to and during presyncope despite the rapid decrease in MSNA (Fu *et al.*, 2012). These individuals may have excessive vasoconstriction in other vascular beds rather than the skeletal muscle. Alternatively, the decrease in MSNA does not lead to a corresponding decrease in total peripheral resistance in them.

In summary, a moderate fall in cardiac output with coincident vasodilatation, or a severe fall in cardiac output without changes in total peripheral resistance contributes importantly to syncope. Sympathetic withdrawal may not always be a prerequisite for neurally mediated syncope. Of note, MSNA analyzed using the conventional methods may not reflect actual changes in sympathetic activity since it is an integrated signal. Analyzing raw nerve signal before integration is needed to confirm these findings.

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References

Ammirati F, Colivicchi F, Santini M. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. Circulation. 2001; 104:52–57. [PubMed: 11435337]

Barcroft H, Edholm OG. On the vasodilatation in human skeletal muscle during posthaemorrhagic fainting. J Physiol. 1945; 104:161–175. [PubMed: 16991676]

Barcroft H, Edholm OG, McMichael J, Sharpey-Shafer EP, Posthaemorrhagic fainting study by cardiac output and forearm flow. Lancet i. Posthaemorrhagic fainting study by cardiac output and forearm flow. Lancet. 1944:489–491.

Bellard E, Fortrat JO, Dupuis JM, Victor J, Leftheriotis G. Haemodynamic response to peripheral venous congestion in patients with unexplained recurrent syncope. Clin Sci (Lond). 2003; 105:331–337. [PubMed: 12725642]

Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. Eur Heart J. 2006; 27:1085–1092. [PubMed: 16569653]

Connolly SJ, Sheldon R, Roberts RS, Gent M. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. J Am Coll Cardiol. 1999; 33:16–20. [PubMed: 9935002]

Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. JAMA. 2003; 289:2224–2229. [PubMed: 12734133]

Cooke WH, Rickards CA, Ryan KL, Kuusela TA, Convertino VA. Muscle sympathetic nerve activity during intense lower body negative pressure to presyncope in humans. J Physiol. 2009; 587:4987–4999. [PubMed: 19703962]

Dietz NM, Halliwill JR, Spielmann JM, Lawler LA, Papouchado BG, Eickhoff TJ, Joyner MJ. Sympathetic withdrawal and forearm vasodilation during vasovagal syncope in humans. J Appl Physiol (1985). 1997a; 82:1785–1793. [PubMed: 9173942]

Dietz NM, Joyner MJ, Shepherd JT. Vasovagal syncope and skeletal muscle vasodilatation: the continuing conundrum. Pacing Clin Electrophysiol. 1997b; 20:775–780. [PubMed: 9080509]

Epstein SE, Stampfer M, Beiser GD. Role of the capacitance and resistance vessels in vasovagal syncope. Circulation. 1968; 37:524–533. [PubMed: 5649078]

Folino AF, Migliore F, Marinelli A, Iliceto S, Buja G. Age-related hemodynamic changes during vasovagal syncope. Auton Neurosci. 2010a; 156:131–137. [PubMed: 20605537]

Folino AF, Russo G, Porta A, Buja G, Cerutti S, Iliceto S. Autonomic modulation and cardiac contractility in vasovagal syncope. Intern J Cardiol. 2010b; 139:248–253.

Fu Q, Verheyden B, Wieling W, Levine BD. Cardiac output and sympathetic vasoconstrictor responses during upright tilt to presyncope in healthy humans. J Physiol. 2012; 590:1839–1848. [PubMed: 22331415]

Fujimura O, Yee R, Klein GJ, Sharma AD, Boahene KA. The diagnostic sensitivity of electrophysiologic testing in patients with syncope caused by transient bradycardia. N Engl J Med. 1989; 321:1703–1707. [PubMed: 2594030]

Gisolf J, Westerhof BE, van Dijk N, Wesseling KH, Wieling W, Karemaker JM. Sublingual nitroglycerin used in routine tilt testing provokes a cardiac output-mediated vasovagal response. J Am Coll Cardiol. 2004; 44:588–593. [PubMed: 15358026]

Goldstein DS, Holmes C, Frank SM, Naqibuddin M, Dendi R, Snader S, Calkins H. Sympathoadrenal imbalance before neurocardiogenic syncope. Am J Cardiol. 2003; 91:53–58. [PubMed: 12505571]

Halliwill JR, Dietz NM, Joyner MJ. Active vasodilation during fainting: a hypothesis revisited. Clin Auton Res. 1996; 6:233–236. [PubMed: 8902320]

Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach J, Joyner MJ. Sex and ageing differences in resting arterial pressure regulation: the role of the beta-adrenergic receptors. J Physiol. 2011; 589:5285–5297. [PubMed: 21859824]

Iwase S, Mano T, Kamiya A, Niimi Y, Fu Q, Suzumura A. Syncopal attack alters the burst properties of muscle sympathetic nerve activity in humans. Auton Neurosci. 2002; 95:141–145. [PubMed: 11871780]

Jardine DL. Vasovagal syncope: new physiologic insights. Cardiol Clin. 2013; 31:75–87. [PubMed: 23217689]

Jardine DL, Melton IC, Crozier IG, English S, Bennett SI, Frampton CM, Ikram H. Decrease in cardiac output and muscle sympathetic activity during vasovagal syncope. Am J Physiol. 2002; 282:H1804–1809.

Kamiya A, Hayano J, Kawada T, Michikami D, Yamamoto K, Ariumi H, Shimizu S, Uemura K, Miyamoto T, Aiba T, Sunagawa K, Sugimachi M. Low-frequency oscillation of sympathetic nerve activity decreases during development of tilt-induced syncope preceding sympathetic withdrawal and bradycardia. Am J Physiol Heart Circ Physiol. 2005; 289:H1758–1769. [PubMed: 15937091]

Kamiya A, Kawada T, Mizuno M, Miyamoto T, Uemura K, Seki K, Shimizu S, Sugimachi M. Baroreflex increases correlation and coherence of muscle sympathetic nerve activity (SNA) with renal and cardiac SNAs. J Physiol Sci. 2006; 56:325–333. [PubMed: 16956421]

Kozlowski D, Byrdziak P, Krupa W, Gawrysiak M, Piwko G, Kubica J, Swiatecka G. Left ventricle systolic volume in vasovagal syncope patients. Folia morphologica. 2003; 62:175–178. [PubMed: 14507042]

Malasana G, Brignole M, Daccarett M, Sherwood R, Hamdan MH. The prevalence and cost of the faint and fall problem in the state of Utah. Pacing Clin Electrophysiol. 2011; 34:278–283. [PubMed: 21029127]

Manyari DE, Rose S, Tyberg JV, Sheldon RS. Abnormal reflex venous function in patients with neuromediated syncope. J Am Coll Cardiol. 1996; 27:1730–1735. [PubMed: 8636561]

Morillo CA, Eckberg DL, Ellenbogen KA, Beightol LA, Hoag JB, Tahvanainen KU, Kuusela TA, Diedrich AM. Vagal and sympathetic mechanisms in patients with orthostatic vasovagal syncope. Circulation. 1997; 96:2509–2513. [PubMed: 9355886]

Mosqueda-Garcia R, Furlan R, Fernandez-Violante R, Desai T, Snell M, Jarai Z, Ananthram V, Robertson RM, Robertson D. Sympathetic and baroreceptor reflex function in neurally mediated syncope evoked by tilt. J Clin Invest. 1997; 99:2736–2744. [PubMed: 9169504]

Moya A, Sutton R, Ammirati F, Blanc JJ, Brignole M, Dahm JB, Deharo JC, Gajek J, Gjesdal K, Krahn A, Massin M, Pepi M, Pezawas T, Ruiz Granell R, Sarasin F, Ungar A, van Dijk JG, Walma EP, Wieling W. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009; 30:2631–2671. [PubMed: 19713422]

Protheroe CL, Dikareva A, Menon C, Claydon VE. Are compression stockings an effective treatment for orthostatic presyncope? PloS one. 2011; 6:e28193. [PubMed: 22194814]

Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J. 2004; 25:1741–1748. [PubMed: 15451153]

Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. Am J Med Sci. 1999; 317:75–77. [PubMed: 10037110]

Salmanpour A, Brown LJ, Shoemaker JK. Detection and classification of raw action potential patterns in human Muscle Sympathetic Nerve Activity. Conf Proc IEEE Eng Med Biol Soc. 2008; 2008:2928–2931. [PubMed: 19163319]

Salmanpour A, Frances MF, Goswami R, Shoemaker JK. Sympathetic neural recruitment patterns during the Valsalva maneuver. Conf Proc IEEE Eng Med Biol Soc. 2011; 2011:6951–6954. [PubMed: 22255937]

Schwartz CE, Lambert E, Medow MS, Stewart JM. Disruption of phase synchronization between blood pressure and muscle sympathetic nerve activity in postural vasovagal syncope. Am J Physiol. 2013; 305:H1238–1245.

Sharpey-Schafer EP. Syncope. Br Med J. 1956; 1:506–509. [PubMed: 13293372]

Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, Levy D. Incidence and prognosis of syncope. N Engl J Med. 2002; 347:878–885. [PubMed: 12239256]

Sra JS, Jazayeri MR, Avitall B, Dhala A, Deshpande S, Blanck Z, Akhtar M. Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. N Engl J Med. 1993; 328:1085–1090. [PubMed: 8455666]

Stewart JM, Lavin J, Weldon A. Orthostasis fails to produce active limb venoconstriction in adolescents. J Appl Physiol (1985). 2001; 91:1723–1729. [PubMed: 11568156]

Stewart JM, McLeod KJ, Sanyal S, Herzberg G, Montgomery LD. Relation of postural vasovagal syncope to splanchnic hypervolemia in adolescents. Circulation. 2004; 110:2575–2581. [PubMed: 15492310]

Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. Circulation. 2000; 102:294–299. [PubMed: 10899092]

Sutton R, Ungar A, Sgobino P, Russo V, Massa R, Melissano D, Beiras X, Bottoni N, Ebert HH, Francese M, Jorfida M, Giuli S, Moya A, Andresen D, Brignole M. Cardiac pacing in patients with neurally mediated syncope and documented asystole: effectiveness analysis from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) Registry. Europace. 2014; 16:595–599. [PubMed: 24406537]

Thomson HL, Atherton JJ, Khafagi FA, Frenneaux MP. Failure of reflex venoconstriction during exercise in patients with vasovagal syncope. Circulation. 1996; 93:953–959. [PubMed: 8598086]

Vaddadi G, Esler MD, Dawood T, Lambert E. Persistence of muscle sympathetic nerve activity during vasovagal syncope. Eur Heart J. 2010; 31:2027–2033. [PubMed: 20304836]

Vaddadi G, Guo L, Esler M, Socratous F, Schlaich M, Chopra R, Eikelis N, Lambert G, Trauer T, Lambert E. Recurrent postural vasovagal syncope: sympathetic nervous system phenotypes. Circ Arrhythm Electrophysiol. 2011; 4:711–718. [PubMed: 21844155]

Verheyden B, Gisolf J, Beckers F, Karemaker JM, Wesseling KH, Aubert AE, Wieling W. Impact of age on the vasovagal response provoked by sublingual nitroglycerine in routine tilt testing. Clin Sci (Lond). 2007; 113:329–337. [PubMed: 17504242]

Verheyden B, Liu J, van Dijk N, Westerhof BE, Reybrouck T, Aubert AE, Wieling W. Steep fall in cardiac output is main determinant of hypotension during drug-free and nitroglycerine-induced orthostatic vasovagal syncope. Heart Rhythm. 2008; 5:1695–1701. [PubMed: 19084808]

Wallin BG, Sundlof G. Sympathetic outflow to muscles during vasovagal syncope. J Auton Nerv Syst. 1982; 6:287–291. [PubMed: 7169498]

Weissler AM, Warren JV, Estes EH Jr. McIntosh HD, Leonard JJ. Vasodepressor syncope; factors influencing cardiac output. Circulation. 1957; 15:875–882. [PubMed: 13437412]