Ethyl Vanillate Levels in Blood and Urine (24-hour Collections)

Day	Plasma Vanillic Acid (Corrected for Normal Phenolic Substances in Blood) (mg./100 ml.)	Urine Vanillic Acid (Calculated as Vanillic and Phenolic Substances Excreted (g.))
28/1/53		1.70
29/1/53		0.88
30/1/53	6.8	5.70
31/1/53		16.50
1/2/53		14.40
2/2/53	3.3	5.75
3/2/53	18.6	26.10
4/2/53	15.8	
5/2/53	20.5	11.40
6/2/53		4.83
7/2/53		6.42
9/2/53	21.5	

Blood levels of over 30 mg. per 100 ml. are apt to cause toxic phenomena (coma with or without convulsions), and if the level exceeds 50 mg. the toxic phenomena can be lethal (Christie *et al.*, 1951). To maintain this blood level in an adult requires about 40 to 50 g. of ethyl vanillate daily by mouth, and in a child 0.75 to 2.5 g. per kg. of body weight a day. More recently, Christie (1952) said that ethyl vanillate was the only therapeutic agent of any value in histoplasmosis, though it was not satisfactory.

The patient here described received 45 g. daily from February 2, but part of this was vomited. From February 5 he received and retained 50 g. daily.

Summary

After a brief review of the cases of histoplasma infection previously published in Great Britain the second case of disseminated histoplasmosis to be reported is described. This case was fatal in spite of treatment with 45–50 g. of ethyl vanillate daily. Some information is included on culture of the organism, as in this case it showed certain cultural peculiarities.

We are grateful for the help we received from many sources in the treatment of this case. We would particularly like to thank Dr. A. S. Osborne, of the American Embassy, Dr. W. P. Kennedy, of the Ministry of Health, and Mr. C. B. Sitterson, jun., of the Institute of Paper Chemistry, Wisconsin, U.S.A., for their advice; Dr. Harvey Blank and Messrs. E. R. Squibb and Sons, New York, U.S.A., for the prompt dispatch to us of ethyl vanillate and appropriate information adequate for the treatment of this case; Dr. R. Forgan, Dr. John Harper, and Messrs. May and Baker, of Dagenham, for their advice and for supplying us with the hydroxy-stilbamidine and "cuprimyl" used by us; Mrs. E. D. Price for her patience and careful secretarial work; and Mr. E. Sheppard for his most excellent photography. Finally, we are most grateful to the nursing staff for the great care with which treatment was carried out, and to Dr. G. H. Cranswick and Dr. P. G. Swann for their many helpful suggestions.

Since this paper was completed we understand that a case of disseminated histoplasmosis in a young woman was transferred to this country from South Africa, where the diagnosis was made. Unfortunately the patient died two days after arrival.

REFERENCES

- Arblaster, P. G. (1950). *Thorax*, **5**, 333.
 Christie, A. (1952). *Lancet*, **1**, 1011.
 — Middleton, J. G., Peterson, J. C., and McVickar, D. L. (1951). *Pediatrics*, **7**, 7.
 Crofton, J. (1950). *Thorax*, **5**, 340.
 Curtis, A. C., and Grekin, J. N. (1947). *J. Amer. med. Ass.*, **134**, 1217.
 Derry, D. C. L., Card, W. I., Wilson, R., and Duncan, J. T. (1942). *Lancet*, **1**, 224.
 Duncan, J. T. (1945). *British Medical Journal*, **2**, 715.
 — (1947). *Trans. roy. Soc. trop. Med. Hyg.*, **40**, 364.
 Ellis, F. F., jun., Scott, R. J., and Miller, J. M. (1952). *Antibiot. and Chemother.*, **2**, 347.
 Hodgson, C. H., Weed, L. A., and Clagett, O. T. (1950). *J. thorac. Surg.*, **20**, 97.
 Hutchison, H. E. (1952). *J. Path. Bact.*, **64**, 309.
 Limerick, C. B. (1951). *British Medical Journal*, **1**, 885.

THE MECHANISM OF SYNCOPE AFTER COUGHING

BY

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Syncope from coughing has been considered a rare condition; thus Whitty (1943) and Baker (1949) could collect only about 100 cases from the literature. Charcot (1876) thought it was a form of epilepsy, and by coining the term "laryngeal vertigo" made it the province of neurology and throat surgery. McCann *et al.* (1949) obtained some continuous records during coughing in two subjects with the syndrome. They believed that syncope was not primarily epileptic but circulatory in origin, and that pulmonary arterial vasoconstriction or pathologically sensitive "vascular reflexes" might be responsible. Correspondence in the *British Medical Journal* resulted in no factual data, but suggested that the condition might be commoner than supposed.

Material and Methods

The patients were 27 middle-aged or elderly males who gave a history of syncopal attacks on coughing. In many it was found possible to provoke an attack by asking the patient to give a few strong coughs. Inhaling cigarette smoke or irritation of the nose was used in a few. Pressures were recorded continuously by capacitance manometers (Hansen, 1949): intrathoracic by means of a water-filled oesophageal tube (Dornhorst and Leathart, 1952); intracardiac by catheter; and intra-arterial and venous by needles or fine catheters. Fore-arm flow was measured with a plethysmograph and recorded on the same photographic paper (Davies, 1953).

Results

The data obtained in the 27 subjects with syncope were compared with similar measurements in about 40 other subjects of all ages and both sexes. There was no qualitative difference in the effects of coughing in the two groups. A single "ahem" produced an intrathoracic pressure rise of 20 to 30 mm. Hg, ordinary coughing in both groups 50 to 100 mm. Hg, and coughing leading to syncope 150 to 300 mm. Hg. The circulatory effects were proportional to the violence and duration of the coughing attacks. All subjects performed the Valsalva manœuvre. There was no difference in circulatory effects after the Valsalva manœuvre between those with cough syncope and those without cough syncope.

Continuous records of syncopal attacks were obtained on fifteen occasions, and many minor attacks causing dizziness or "blackout" were also recorded. The subjects coughed in two ways, continuous or intermittent, with different circulatory effects. Both, when violent, resulted in syncope.

Continuous Coughing

The subjects coughed continuously in prolonged paroxysms lasting many seconds without drawing breath. Often the intrathoracic pressure reached 300 mm. Hg and was maintained at this level until a breath was taken or the paroxysm ended. The circulatory effects were essentially similar to those of the Valsalva manœuvre, but more pronounced owing to the greater rise of intrathoracic pressure. When asked to perform their maximum Valsalva manœuvre it was found that few could reach and maintain an intrathoracic pressure of 100 mm. Hg. This conspicuous

FIG. 1.—An example of continuous coughing lasting many seconds. The large downward deflection in arterial and superior vena caval pressures during the attack are due to occasional inspirations. Consciousness was lost at the end of the attack, when arterial pressure was lowest. Time marker in seconds in this and subsequent records.

difference between coughing and the Valsalva manoeuvre may result from the greater number of muscles and the more powerful intermittent muscular effort employed in coughing.

An example of syncope from continuous coughing is shown in Fig. 1. Unconsciousness resulted when arterial pressure was lowest at the end of the attack. As in other forms of syncope from acute arterial hypotension (Barcroft *et al.*, 1944; Brigden *et al.*, 1950; Howard *et al.*, 1951; Howarth and Lowe, 1953) the critical level for loss of consciousness was about 50 mm. Hg. Twitching movements and convulsions were common during syncope.

Two subjects were observed to become unconscious, as judged by rolling up of the eyes and twitching movements, during coughing, while intrathoracic and arterial pressures were still greatly elevated. Catheters passed high up the internal jugular vein showed that intrathoracic pressure changes were fully transmitted to the venous outflow of the brain. As can be seen in Fig. 1, the arterio-venous pressure difference across the brain may reach its lowest level during the paroxysm.

Intermittent Coughing

This was the "normal" form of coughing, inspiration following each cough in a fairly regular sequence. It caused large rapid fluctuations in intrathoracic pressure, which will be termed "cough transients." It was followed in all subjects by a fall of arterial pressure. An example of syncope from this form of coughing is shown in Fig. 2. Consciousness was lost at the lowest blood-pressure level.

Physiological Effects of Coughing

Fig. 3 summarizes the changes caused by the Valsalva manoeuvre (or continuous coughing) and intermittent coughing. The data have been published elsewhere (Sharpey-Schafer, 1953). A to B is the period of raised intrathoracic pressure. This pressure is transmitted to the arteries, veins without valves, and the chambers of the heart. In the periphery, venous valves shut and blood accumulates distal to them at a rate which depends on previous vasomotor tone (Howard *et al.*, 1951) and the height to which the arterial supply pressure is raised.

The accumulation of blood in peripheral veins results in a decrease in the filling pressure of the heart and subsequent fall in stroke output. Pulse pressure is decreased in peripheral arteries during the Valsalva manoeuvre or continuous coughing, but large cough transients are the conspicuous feature of arterial records in intermittent coughing. Baroreceptors therefore are exposed to diminished pulsations during the Valsalva manoeuvre and to large

pressure transients during intermittent coughing. In the former case the response is peripheral constriction and in the latter dilatation, as shown in the forearm during the period B to D. These blood-flow changes do not occur in sympathectomized limbs, and are therefore mediated through the vasomotor nerves. The suggestion that these circulatory responses result from decreased or increased stimulation of baroreceptors by rapid transients is supported by recent work on the isolated carotid sinus of the dog (Ead *et al.*, 1952).

There is a further important difference between the Valsalva manoeuvre and intermittent coughing. In the former at point B the intrathoracic pressure falls immediately to the control level; in the latter it is elevated 10 or more mm. Hg (Fig. 3) and may remain so for many seconds during the period B to D. This raised pressure is transmitted to the chambers of the heart and great veins (Fig. 4) and may play a part in the production of post-tussive arterial hypotension by reducing cardiac output below control values, since it can be shown that positive-pressure breathing causes a fall in cardiac output (Werkö, 1947). There was no evidence on measurement of pulmonary arterial vasoconstriction as suggested by McCann *et al.* (1949).

Clinical Considerations

Some knowledge of the causes of this form of syncope has been helpful in the interpretation of symptoms. If normal physiological mechanisms only were involved it seemed unlikely that the condition was rare. The 27 cases investigated were found without difficulty over a period of two years and many others were seen clinically. Indeed, minor symptoms such as dizziness are almost universal among those who cough strongly. The curious rarity of the

FIG. 2.—Arterial pressure record of intermittent coughing. Large arterial cough transients were followed by hypotension and syncope.

syndrome in females may be due, in part, to social taboos which impose the belief that such exhibitions of violence are "unladylike." The case of a Scots woman with typical attacks has, however, been reported to me. Continuous records are not yet available from children with whooping-cough and infants with breath-holding.

FIG. 3.—Diagrammatic representation of the circulatory events caused by the Valsalva manœuvre or continuous coughing, and intermittent coughing (see text). The changes in left ventricular output were not measured directly but were inferred from the arterial records.

Patients with large quantities of sputum from chronic pulmonary disease rarely show these symptoms. Continuous records during coughing in such patients showed that intrathoracic pressure rose no higher than about 100 mm. Hg, and although the usual circulatory changes were present they were not sufficiently pronounced to interfere with the blood supply to the brain.

The role of smoking, drinking, and bad teeth and other infections is to produce the upper respiratory tickle, which, like some forms of skin itching, needs the utmost violence to assuage. This form of coughing may become a habit. It is easy to see why middle-aged males are the chief victims.

A history of a single cough followed by immediate unconsciousness should be regarded with suspicion. Three of the subjects reported here gave such a history, but proved to have typical attacks of prolonged violent coughing followed by syncope. Questioned after a recorded attack, they still claimed immediate unconsciousness.

Two may have had a short period of retrograde amnesia; the third interpreted 15 seconds as "immediate."

The occurrence of fits during syncope after coughing is likely to be more misleading than to circulatory workers, who are probably aware that a fit can occur in any normal subject if the blood flow to the brain is sufficiently reduced. If the subject is a known epileptic the full seizure is more easily induced by methods of lowering the blood pressure. Two of the present cases had a history of epilepsy and grand mal after violent coughing.

The appearance of the subject during continuous violent coughing is alarming, and may suggest to the lay and even the medical mind the likelihood of a burst blood vessel,

while the subsequent syncope may indicate that this calamity has occurred. The vessels of internal organs such as the brain, however, are protected from high pressure differences across their walls, since surrounding structures are exposed to the same pressure, and, as explained above, the pressure across these vessels is less, not more, than normal.

It is only in places where veins are in near contact with the outside atmosphere that pressure differences of 300 mm. Hg may be built up. Since surface veins are protected by valves, high pressures are reached only after a period of some seconds. In prolonged paroxysms of coughing nose veins commonly burst, and occasionally veins in the conjunctiva and anus do likewise.

Treatment

Attempts to alter bad habits or causal irritant factors proved singularly unsuccessful in this group of middle-aged men. Explanation of the mechanism was tried with more intelligent subjects, but even these found it difficult to realize that extreme violence was unnecessary and clung to their way of coughing for various fanciful and erroneous reasons.

The investigation, however, showed a method which, while annoying to the investigator, was almost uniformly successful in alleviating the attacks. It was found on the first occasion when measurements were made that an attack could be induced with ease. Subsequently more and more encouragement became necessary to produce the required intrathoracic pressure changes. The subjects learnt by demonstration that it was violence which caused syncope. As one said on the fifth occasion, "I don't see why I should cough myself unconscious any more—to please you, Doctor."

Summary

Syncope from coughing was found to be common and to result from an acute diminution of supply pressure of blood to the brain. Continuous records in 27 cases indicated that normal physiological mechanisms only

FIG. 4.—Upper curve, intra-oesophageal (intrathoracic) pressure; lower curve, pulmonary artery pressure. Both were elevated to the same extent after coughing.

were involved. The violence of the coughing was the determining factor, intrathoracic pressures of 200 to 300 mm. Hg being reached.

Subjects who coughed continuously without drawing breath were shown to have circulatory changes which were exaggerated examples of the effects of the Valsalva manœuvre. Consciousness was usually lost during the period of acute hypotension following cessation of coughing. Occasionally syncope occurred while intrathoracic pressure was still high, but the arterio-venous pressure difference across the brain was greatly reduced.

Subjects who coughed intermittently also had syncope. Arterial pressure and peripheral blood flow records showed vasodilatation following this form of coughing in contrast to the vasoconstriction which resulted from the Valsalva manoeuvre and continuous coughing.

It is suggested that vasodilatation following intermittent coughing is due to the stimulation of baroreceptors by large arterial cough transients.

Intrathoracic pressure remained elevated about 10 mm. Hg for many seconds following intermittent coughing.

REFERENCES

- Baker, C. (1949). *Guy's Hosp. Rep.*, 98, 132.
 Barcroft, H., Edholm, O. G., McMichael, J., and Sharpey-Schafer, E. P. (1944). *Lancet*, 1, 489.
 Brigden, W., Howarth, Sheila, and Sharpey-Schafer, E. P. (1950). *Clin. Sci.*, 9, 79.
 Charcot, J. M. (1876). *Leçons sur les Localisations dans les Maladies de Cerveaux*, 1. 1. Paris, aux Bureaux du Progrès médical.
 Davies, J. G. (1953). *J. sci. Instrum.* (In press.)
 Dornhorst, A. C., and Leathart, G. L. (1952). *Lancet*, 2, 109.
 Ead, H. W., Green, J. H., and Neil, E. (1952). *J. Physiol., Lond.*, 118, 509.
 Hansen, A. T. (1949). *Pressure Measurement in the Human Organism*. Teknisk Forlag, Copenhagen.
 Howard, P., Leathart, G. L., Dornhorst, A. C., and Sharpey-Schafer, E. P. (1951). *British Medical Journal*, 2, 382.
 Howarth, Sheila, and Lowe, J. B. (1953). *Brit. Heart J.*, 15, 47.
 McCann, W. S., Bruce, R. A., Lovejoy, F. W., jun., Yu, P. N. G., Pearson, R., Emerson, E. B., Engel, G., and Kelly, J. J. (1949). *Arch. intern. Med.*, 84, 845.
 Sharpey-Schafer, E. P. (1953). *J. Physiol.* (In press.)
 Werkö, L. (1947). *Acta med. scand.*, Suppl. 193, p. 1.
 Whitty, C. W. M. (1943). *Brain*, 66, 43.

EFFECTS ON BLOOD PRESSURE OF VENTRICULAR ASYSTOLE DURING STOKES-ADAMS ATTACKS AND ACETYLCHOLINE INJECTIONS

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Ventricular standstill may occur spontaneously in cases of heart-block, and during Stokes-Adams attacks consciousness is lost if asystole is sufficiently prolonged. Cardiac arrest also follows the intravenous injection of acetylcholine, with resulting loss of consciousness (Phillips *et al.*, 1952). Observations have been made to determine the peripheral arterial pressure in these two types of case, and the results are reported in this paper.

Blood pressure was recorded continuously in the brachial artery, using a capacitance manometer (Hansen, 1949). The Stokes-Adams attacks occurred spontaneously in a patient with heart-block, who later showed no macroscopic heart lesion at necropsy. Rapid intravenous injections of 50 to 200 mg. of acetylcholine chloride were given as a part of routine therapy to psychoneurotic patients who had no organic circulatory abnormality on clinical examination.

Results

The blood-pressure records in both types of case show a striking similarity. Typical examples are shown in Figs. 1 and 2. Ventricular asystole was always followed by an acute

fall in blood pressure. With prolonged standstill, blood pressure fell rapidly at first, then more slowly, and finally remained constant at about 20–25 mm. Hg. Loss of consciousness was often followed by convulsive movements.

When ventricular contractions were resumed an "overshoot" was seen on all blood-pressure records: systolic and diastolic pressures rose above control levels for a variable number of seconds before the blood pressure returned to normal. An increase in pulse pressure, more striking in the Stokes-Adams attacks, was recorded during the overshoot. The characteristic flush which accompanied restoration of the circulation following the Stokes-Adams attacks was also observed after cardiac arrest from acetylcholine injection.

FIG. 1.—Effects on the blood pressure of a Stokes-Adams attack. Above: Lead II of the electrocardiogram. Convulsive movements produced interference with the record after 16 seconds asystole. Below: Continuous brachial arterial pressure record. Time (top) in seconds. Calibration in mm. Hg.

FIG. 2.—Effect on the blood pressure of cardiac arrest produced by 100 mg. of acetylcholine given intravenously. Period of injection is shown by signal on time marker. Time in seconds.

Discussion

In spontaneous and induced ventricular asystole, blood pressure falls rapidly to syncopal levels. Systemic arterial pressure tends to stabilize during cardiac standstill at 20–25 mm. Hg. This figure does not differ greatly from the standing pressure of 14 to 22 mm. Hg observed by Dowling *et al.* (1952) during asystole induced for 5 to 10 seconds by carotid sinus pressure. These authors, however, did not record a subsequent overshoot in the systemic pressure.

The overshoot may be regarded as a response to the lowered blood pressure. A similar overshoot follows the fall in effective systemic pressure during the Valsalva manoeuvre (Hamilton *et al.*, 1936; Howard *et al.*, 1951), where it has been shown to be due to sympathetic vasoconstriction (Wilkins and Culbertson, 1947). Vasoconstriction has been demonstrated in muscle vessels during the overshoot of the Valsalva manoeuvre (Howard *et al.*, personal communication); but vasodilatation may be present in the vessels of the skin during the overshoot after asystole, since vivid flushing of the face and neck occurs in both Stokes-Adams attacks and after intravenous acetylcholine injection.

The striking similarity between acetylcholine-induced asystole and spontaneously occurring Stokes-Adams attacks suggests that these effects of intravenous acetylcholine injections result from asystole alone.