Cardiovascular Risk: The Safety of Local Anesthesia, Vasoconstrictors, and Sedation in Heart Disease

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As part of a large pragmatic study, the authors investigated heart rate, blood pressure, dysrhythmic and ischemic responses to lidocaine 2% with a combination vasoconstrictor (noradrenaline 1 : 50,000 and vasopressin 0.25 IU/mL), and midazolam sedation in a medically compromised population. There were anesthesia-induced physiological changes to both hemodynamics and the electrocardiogram. The use of midazolam significantly ameliorated the sympathoadrenal response to stress, and the greatest hemodynamic and electrocardiographic changes were observed during surgery.

Key Words: Electrocardiography; Heart disease; Local anesthetics; Midazolam; Noradrenaline; Vasopressin.

Local anesthesia is a universal method of pain control, and its popularity is a testament to efficacy and safety. Plain lidocaine is an evanescent drug,[1] so for dental practice, vasoconstrictors are routinely incorporated to improve both the depth and duration of analgesia and to secure hemostasis.[2,3] Current clinical practice tacitly accepts the safety of adrenaline in patients with cardiovascular disease,[4] but strong reservations have been expressed for the similar employment of noradrenaline.[4,5,6] However, the combination of a catecholamine and a posterior pituitary analog should act synergistically on both arterial and venous aspects of the capillary bed.[7] This synergy might permit an effective reduction to the concentration of one or both agents without compromise to vasoconstrictor potency and a consequent improvement to the management of cardiovascular risk.

Anxiety, fear, anesthesia, and surgery are all accompanied by psychological, physiological, and biochemical changes.[8] The following are but a limited selection from the literature to illustrate the true diversity of responses to local anesthetics with vasoconstrictors. These responses include changes to heart rate (HR) and blood pressure,[9,10] changes to cardiac rhythm and electrocardiographic ST-segment wave,[11,12] endogenous catecholamine release,[13] endocrine response to surgery,[14] and hypokalemic response to local analgesia.[15] These changes are regulated by the net balance between sympathetic and parasympathetic activity, and in addition to pharmacological modification, there is evidence that the autonomic response is further influenced by both stress and pain.[16] All these events imply a certain morbidity, which has in the past been frequently extrapolated to the more susceptible population by means of citing the dangers inherent in the combination of dental stress, local anesthesia, and exogenous and endogenous catecholamines.[10,17–19] However, these reservations have often been poorly voiced and may in general apply to a medically compromised population or, in particular, to the use of catecholamine vasoconstrictors.[6]

METHODS

As part of a large investigation (R. J. Middlehurst, unpublished data, 1999), this randomized, blinded, controlled, and comparative study investigated hemodynamic and electrocardiographic responses to lidocaine 2%, noradrenaline 1 : 50,000, vasopressin 0.25 IU/mL, and midazolam. Seventy-five patients with heart disease (American Society of Anesthesiologists Cate-

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Hemodynamic Data for Local Anesthetic and Sedation Groups*

Phase of Investigation	*Lidocaine 2%, Noradrenaline 1 : 50,000, and Vasopressin 0.25 IU/mL*		*Lidocaine 2%, Noradrenaline 1 : 50,000, Vasopressin 0.25 IU/mL, and Midazolam*	
	HR, bpm†	*SBP, mm Hg*	*HR, bpm*	*SBP, mm Hg*
Stabilization	77.3 ± 7.8	142.9 ± 12.2	74.6 ± 8.6	137.7 ± 10.6
Anesthesia	75.3 ± 2.5	154.9 ± 4.8	66.5 ± 7.5	135.8 ± 6.6
Surgery	75.3 ± 2.0	153.4 ± 4.7	69.0 ± 5.0	131.1 ± 8.0
Recovery	75.1 ± 1.7	141.9 ± 3.3	68.4 ± 5.0	121.1 ± 7.3
Sedation	. . .	. . .	77.7 ± 2.5	113.7 ± 6.6

* Mean values ± SD.
† HR indicates heart rate; bpm, beats per minute; and SBP, systolic blood pressure.

gories III and IV) were prescribed dentoalveolar surgery using lidocaine 2%, noradrenaline 1 : 50,000, and vasopressin 0.25 IU/mL. For 25 of these patients, analgesia was supplemented by intravenous midazolam.

A noninvasive pulse and blood pressure monitor with integral printer (Datascope Accutor I, Datascope Corporation, Paramus, NJ) was used to record hemodynamics at 1-minute intervals through the 5 phases of treatment, defined as stabilization, sedation (when used), anesthesia, surgery, and recovery. Patients were placed in a semirecumbent position, a cuff of suitable width was applied, and recording started. After 5 minutes, the baseline reading was taken, followed by at least 30 consecutive measurements. All surgical procedures were performed by 1 operator. Hemodynamic data were stored on a mainframe computer (Amdhal 5890/300) and analyzed using repeated measurements analysis of variance from the Statistical Package for the Social Sciences (SPSS, Version 4.0), commercially available software (Fortran 77, Ghost 80), and designer software (Medplot) to plot a confidence interval framework, with Mauchly Sphericity and Pillai tests for intra- and intergroup comparison. An ambulatory electrocardiogram (ECG) recorder (Holter Tracker) and Reynolds Medical Pathfinder 3 (Model P31 High Speed ECG Analyser) were used to tape and evaluate rhythm and ischemic change. These data were analyzed using nonparametric statistical tests, including Friedman, Mann-Whitney, and Kruskal-Wallis. Finally, the study was conducted with the approval of the Hospital Ethics Committee in accord with the Declaration of Helsinki.

RESULTS

The following general data were recorded for the 50 patients in the local anesthetic group. The mean age was 58.3 years, SD ± 11.0. There were 41 male and 9 female subjects. Cardiac pathology was derived from the World Health Organization Index for Cardiac Disease. Nine subjects (18%) had valvular heart disease, 14 (28%) had hypertension, 23 (46%) experienced ischemia, 1 (2%) had cardiomyopathy, 1 (2%) had cardiac dysrhythmias, and 2 (4%) had heart failure. The mean quantity of local anesthesia was 4.9 ± 2.0 mL. Hypotensive therapy (β blockers, calcium channel antagonists, diuretics, vasodilators, and angiotensin-converting enzyme inhibitors) was administered to 22 subjects (44%). The duration of surgery was 15.5 ± 10.4 minutes, and 2 patients (4%) experienced dental pain during surgery.

The same data were collected for the 25 patients in the sedation group. The mean age was 57.7 years, SD ± 13.6. There were 15 male and 10 female subjects. One subject (4%) had rheumatic heart disease, 1 (4%) had valvular problems, 4 (16%) had hypertension, 17 (68%) were ischemic, 1 (4%) had cardiac dysrhythmias, and 1 (4%) had a heart transplant. The mean quantity local anesthesia was 5.5 ± 1.4 mL. The mean quantity of sedation was 6.4 ± 1.8 mg. Hypotensive therapy was administered to 16 patients (64%), and the duration of surgery was 20.0 ± 10.4 minutes. One patient (4%) experienced pain.

For the local anesthetic group, there were statistically significant changes to the individual parameters of mean HR (−2.6%, $P < .01$) and mean systolic blood pressure (+8.4%, $P < .01$) with the administration of anesthetic (Table; Figures 1 and 2). Graphically, the results for systolic blood pressure formed a peaked data profile that was time dependent, rising from a baseline value to a peak and then falling. This pattern of response generates interest in the peak, which may be related to the maximum effect of the given agent. However, despite this profile, there were no significant differences between the individual phases of treatment.

For the ECG, a total of 181,765 electrocardiographic wave (QRS) complexes were counted and analyzed, and 1333 (0.73%) proved to be dysrhythmic. A total of 43.8% of dysrhythmias occurred during the investigated phases and affected 50.0% of patients in the group:

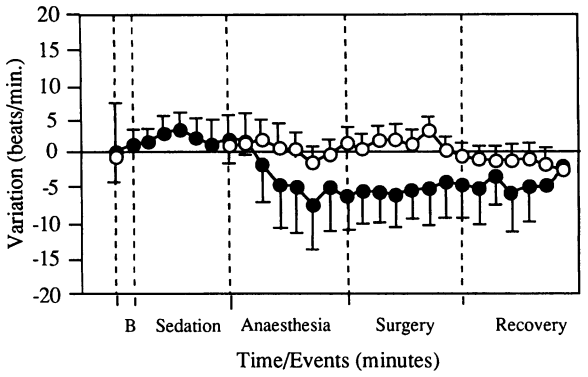

Figure 1. Heart rate profiles (variation from baseline). ○ indicates lidocaine, noradrenaline, and vasopressin; ●, lidocaine, noradrenaline, vasopressin, and midazolam; bars, 95% confidence interval.

18.9% during stabilization, 22.4% during local anesthesia, 36.2% during surgery, and 22.4% during recovery. The main dysrhythmias were premature ventricular beats (29.8%), ventricular ectopics (37.5%), and complex ventricular beats (8.3%) and pauses (8.3%). A total of 97.3% were benign, whereas 2.7% were malignant. Statistically, there were no significant differences between the phases of treatment. No patients had significant displacement to the ST segment (diagnosed as a shift equal to or greater than a 1-mm 0.15 mV).

For the sedation group, midazolam induced significant changes to the parameters of HR (+4.1%, $P < .01$) and systolic blood pressure (SBP; −17.4%, $P < .01$). The administration of anesthetic then induced further significant changes in HR (−14.0%, $P < .01$) and SBP (+19.4%, $P < .01$). However, there were again no significant differences between the phases of treatment (Table; Figures 1 and 2).

For the ECG, a total of 88,124 QRS complexes were counted and analyzed; 769 (0.87%) proved to be dysrhythmic. A total of 15.9% of dysrhythmias occurred during the investigated phases and affected 52.0% of patients in the group. A total of 23.9% occurred during stabilization: 20.7% during sedation, 21.5% during local anesthesia, 25.2% during surgery, and 8.6% during recovery. The main dysrhythmias were premature ventricular beats (20.0%), ventricular ectopics (32.0%), and complex ventricular beats (8.0%). Of these, 94.3% were benign and 5.7% were malignant. Again, there were no significant differences between the phases of treatment. Three patients (12%) exhibited significant displacement to the ST segment.

There were no significant differences between the anesthetic and sedation groups for HR, but midazolam significantly attenuated SBP ($P < .01$) for the phases of anesthesia, surgery and recovery. For electrocardiography in the anesthetic group, 33% of the total number of ventricular ectopics (37.5% of benign arrhythmias) and, for the sedation group, 39% of the total number of ventricular ectopics (15.5% of benign arrhythmias), were accounted for by a single individual in each group, which precluded accurate comparison. Malignant arrhythmic activity increased marginally with the use of midazolam, from 2.7 to 5.7%. Dysrhythmic activity for both groups was greatest during the phase of surgery.

However, all these events represented an average effect, and although some members of the trial population might have experienced a greater improvement to outcome, some might not. The extreme responders (the individuals with the greatest change in HR, SBP, or ECG during the phase of local anesthesia) were as follows: in the local anesthetic group, the greatest change

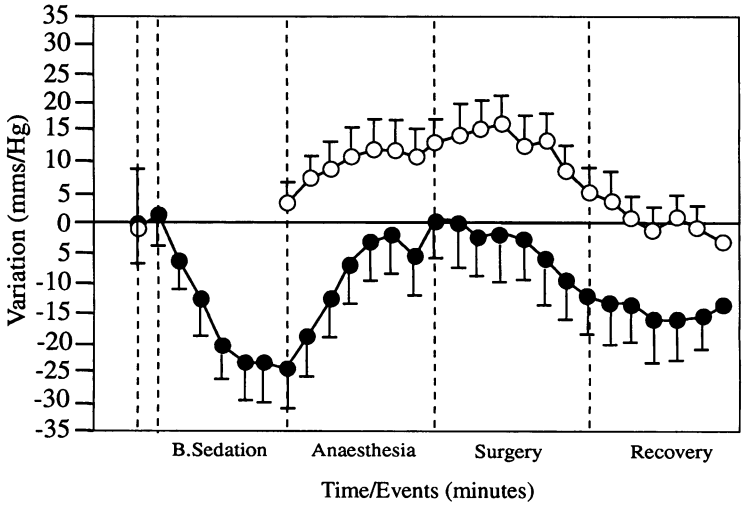

Figure 2. Systolic blood pressure profiles (variation from baseline). ○ indicates lidocaine, noradrenaline, and vasopressin; ●, lidocaine, noradrenaline, vasopressin, and midazolam; bars, 95% confidence interval.

to HR, from 104 to 168 beats per minute (bpm; mean = 123) occurred in a 34-year-old woman with hypertensive heart disease and insulin-dependent diabetes. The local anesthetic volume was 4 mL. She received no hypotensive therapy. We surgically removed a wisdom tooth; the surgery duration was 18 minutes, and she experienced no pain. The greatest change to SBP, from 150 to 194 mm Hg (mean = 173) occurred in a 69-year-old man with hypertensive heart disease, chronic obstructive airways disease, and insulin-dependent diabetes. Local anesthetic volume was 8 mL. He received no hypotensive therapy and underwent surgical exodontia for 5 teeth. The surgery duration was 15 minutes, and he experienced no pain. The greatest change to the ECG, 35 ventricular ectopic (VE) beats (7.0% of total VE for the group, rate = 2.4 bpm; other arrhythmias, 1 couplet, 46 premature supraventricular beats, a single pause, and no ST segment deviation; HR, mean = 92.8 bpm, maximal = 97 bpm; SBP, mean = 104 mm Hg, maximal = 111 mm Hg), occurred in a 52-year-old male with valvular heart disease, taking no medication. The local anesthetic volume was 8.5 mL. He underwent dental clearance. The surgery duration was 23 minutes, and he felt no pain.

In the sedation group, the greatest change to HR, from 91.2 to 120 bpm (mean = 115) occurred in a 4-year-old girl with cardiac dysrhythmia. She took 6 mg midazolam. The local anesthetic volume was 3 mL. She received no hypotensive therapy and underwent an apicoectomy, which lasted 14 minutes. She experienced no pain. The greatest change to SBP, from 129 to 152 mm Hg (mean = 135) occurred in a 57 year-old-man with a heart transplant. He took 8 mg midazolam. The local anesthetic volume was 8 mL. He received no hypotensive therapy and underwent surgical removal of 4 teeth. The procedure lasted 22 minutes, and he experienced no pain. The greatest change to the ECG, 22 VE beats, (4.9% of total VE for the group, rate = 2.2 bpm; other arrhythmias, 2 pauses, no ST segment changes; HR, mean = 55 bpm, maximal = 59 bpm; SBP, mean = 134 mm Hg, maximal = 150 mm Hg), occurred in a 74-year-old male with hypertension and a β-blockade. He took 10 mg midazolam. The local anesthetic volume was 6 mL. He underwent a maxillary sequestrectomy, which lasted 14 minutes, and he felt no pain.

The frequency for successful analgesia with lidocaine, noradrenaline, and vasopressin, defined as surgery without pain, was excellent at 96% for both the anesthetic and sedation groups.

DISCUSSION

Though local anesthesia induced statistically significant changes to the mean values for HR and SBP for both anesthetic and sedation groups, the physiological magnitude and clinical relevance of such change would best be described as minimal. Maximal values were seen during the phase of surgery and were consistent with the observations of Knoll-Kohler et al[20] and Paramaesvaran and Kingon.[21] Greater hemodynamic changes have been reported for cardiac patients with controlled maximal exercise and isometric muscle testing.[22,23] However, there were no significant differences between the phases of treatment. Thus to patients with cardiovascular disease, the administration of the local anesthetic appeared to be no more stressful than the phases of stabilization, surgery, or recovery; conversely, to the patient, stabilization, surgery, and recovery were as stressful as anesthesia.

For the ECG, dysrhythmias were common, but their incidence was low. Previous dental studies have been confused on this particular issue, reading significance into prevalence[24] and excluding patients of particular interest—for example, those with known dysrhythmias and ischemic heart disease.[25] However, dynamic electrocardiography has demonstrated the ubiquity of arrhythmias and ischemic change in the general population. Arrhythmias have been recorded in 56% of fit medical students[26] and 90% of individuals with coronary heart disease.[27] Changes in ST segments and T waves have been recorded in 23% of unaffected subjects[28] and 90% of individuals with coronary heart disease.[29] A better judgment on prognosis might therefore be offered by the known hierarchy of risk associated with the more complex or malignant arrhythmia,[30] defining dysrhythmias such as premature supraventricular beats, ventricular ectopics, and pauses as benign and atrial bigeminy, trigeminy, multiple consecutive beats, and sustained supraventricular and ventricular tachycardias as malignant. However, such malignant arrhythmias have also proven to be almost omnipresent in the general population.[26,27] A number of investigators have looked further for other predictors of sudden cardiac death, without great result apart from the repetition of known associations with heart disease, ischemia, chronic ectopic activity, catecholamine release, circadian rhythm, potassium levels, mental stress, and physical activity.[31,32] For this investigation, what was surprising was that up to 42% of the total arrhythmic data was accounted for by a single individual and that though dysrhythmias were scattered across all phases of treatment, they were most common during surgery. The latter was also an observation made by Barkin and Middleton.[33] Finally, the use of midazolam sedation improved hemodynamics whether measured in a summarized or extreme manner, but it marginally increased malignant arrhythmic activity, apparently at the expense of benign activity.

As to noradrenaline, there is little pharmacological ar-

gument for the employment of this particular catecholamine as a vasoconstrictor. Its potency is a quarter that of adrenaline,[34] and because of its tendency to induce hypertensive change, the majority of investigators have always suggested that it should not be employed in such a role.[4,6,35,36] However, in the main study (R. J. Middlehurst, unpublished data, 1999) there was a rank order for the prevalence of arrhythmias with lidocaine anesthesia that was dependent upon adrenaline concentration. Greatest for the combination vasoconstrictor was adrenaline 1 : 50,000 and vasopressin 0.25 IU/mL; intermediate was lidocaine with adrenaline 1 : 80,000; and least was the adrenaline-free combination of noradrenaline 1 : 50,000 and vasopressin 0.25 IU/mL. This may be explained by adrenaline's major effect as a cardiac stimulant, inducing a tachycardia and, as a consequence, ischemia. Finally, the hemodynamic changes for the extreme responders might represent the capture of intravascular injection sequelae, and a literature review reported the risk for such events at 8%.[37]

The hypothesis argued for the risks of local anesthesia in heart disease is that structural and functional abnormalities have the potential to interact with external triggers, alone or in synergy, to produce the common end point of sudden cardiac stress or death. For dentistry, this remains a simplistic point of view, given the scale of local anesthetic use, with Lilley et al suggesting that in 1978 approximately 70 million injections were given in the United Kingdom.[38] Yagiela has also reported that mortality over a 30-year period ranged from 1 death in 1.4 million to 1 death in 45 million administrations.[39] However, circulatory diseases have been described as the epidemic of our time[40] and are more prevalent with age, and the elderly are a group who will in the future require increasing dental care.[41] It is this context that gives relevance to an information gap regarding the safety of local analgesia.

This study dealt with patients of marked medical compromise. Most were on waiting lists for cardiac surgery and underwent challenging surgical dentistry with substantial quantities of local anesthetic. The resultant hemodynamic and electrocardiographic changes were not clinically significant. Conscious sedation with intravenous midazolam attenuated the sympathoadrenal response, and greater changes were always seen during the phase of surgery. Professional attention should therefore be directed to the management of the whole patient episode, not just perceived problems with the administration of anesthesia.

CONCLUSION

It is recommended that clinical practice for local anesthesia in patients with cardiovascular disease should follow established protocols for risk minimization with (a) sensible prescribing for dental treatment, eg, prophylactic and restorative solutions in preference to surgical intervention; (b) behavioral modification; (c) the use of reasonable quantities of a local anesthetic, such as lidocaine 2% with adrenaline at its minimally effective concentration; (d) aspiration on injection; and (e) appropriate monitoring. Finally, the protocol should include the prescription of a sedative agent, such as midazolam, for its attenuation of the sympathoadrenal response.

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REFERENCES

1. Yagiela JA. Local anaesthetics: a century of progress. *Anesth Prog.* 1985;32:47–56.

2. Roberts DH, Sowray JH. *Local Analgesia in Dentistry.* Bristol, England: Wright; 1987:30.

3. Jastak JT, Yagiela JA. Vasoconstrictors and local anaesthesia: a review and rationale for use. *J Am Dent Assoc.* 1983;107:623–629.

4. Cawson RA, Curson I, Whittington DR. The hazards of dental local anaesthetics. *Br Dent J.* 1983;154:253–258.

5. Boakes AJ, Laurence DR, Lovel KW, O'Neill R, Verrill PJ. Adverse reactions to local anaesthetic/vasoconstrictor preparations. *Br Dent J.* 1972;133:137–139.

6. Van der Bijl P, Victor AM. Adverse reactions associated with norepinephrine in dental local anaesthesia. *Anesth Prog.* 1992;39:87–89.

7. Bartlestone HJ, Nasmyth PA. Vasopressin potentiation of catecholamine actions in dog, rat, cat and rat aortic strip. *Am J Physiol.* 1965;208:754–762.

8. Hempenstall PD, Campbell JPS, Bajurnow AT, Reade PC, McGrath B, Harrison LC. Cardiovascular, biochemical and hormonal responses to intravenous sedation with local analgesia versus general anaesthesia in patients undergoing oral surgery. *J Oral Maxillofac Surg.* 1986;44:441–446.

9. Cheraskin E, Prasertsuntarasai T. Use of epinephrine with local analgesia in hypertensive patients. *J Am Dent Assoc.* 1959;58:507–519.

10. Brand HS, Abraham-Inpijn L. Cardiovascular responses induced by dental treatment. *Eur J Oral Sci.* 1996;104:245–252.

11. Summers L. An investigation into the effects of surgical stress on the fit and poor-risk patient including the modifying effects of relative analgesia and beta blockade. *Br J Oral Surg.* 1981;19:3–12.

12. Hasse AL, Heng MK, Garrett NR. Blood pressure and electrocardiographic response to dental treatment with use of local anaesthesia. *J Am Dent Assoc.* 1986;113:639–642.

13. Edmondson HD, Roscoe B, Vickers MD. Biochemical evidence of anxiety in dental patients. *Br Med J.* 1972;4:7–9.

14. Chernow B, Higgins T. The endocrine and metabolic responses to the stresses of anesthesia and surgery. In: Scurr C, Feldmann S, Soni N, eds. *Scientific Foundations of Anaesthesia.* Oxford, England: William Heinmann; 1990:354–359.

15. Kubota Y, Toyoda Y, Kubota H, Asada A. Epinephrine in local anaesthetics does indeed produce hypokalaemia and ECG changes. *Anesth Analges.* 1993;77:867–868.

16. Heller PH, Perry F, Naifeh K, Gordon NC, Wachter-Shikura N, Levine J. Cardiovascular autonomic response during preoperative stress and postoperative pain. *Pain.* 1984; 18:33–40.

17. Malamed SF. *Handbook of Local Anesthesia.* 3rd ed. St Louis, Mo: Mosby Year-Book; 1990:287.

18. Lipp M, Daublander M. Aspects of local anesthesia in patients with coronary heart disease. *Quintessenz.* 1991;42: 983–990.

19. Perrusse R, Goulet JP, Turcotte JY. Contraindications to vasoconstrictors in dentistry: part I. Cardiovascular diseases. *Oral Surg Oral Med Oral Path.* 1992;74:679–686.

20. Knoll-Kohler E, Knoller M, Brandt K, Becker J. Cardiohemodynamic and serum catecholamine response to surgical removal of impacted third molars under local anesthesia: a randomized double-blind parallel group and crossover study. *J Oral Maxillofac Surg.* 1991;49:957–962.

21. Paramaesvaran M, Kingon AM. Alterations in blood pressure and pulse rate in exodontia patients. *Aust Dent J.* 1994;39:282–286.

22. Ehansi AA, Ogawa T, Miller TR, Spina RJ, Jilka SM. Exercise training improves left ventricular function in older men. *Circulation.* 1991;83:96–103.

23. Lind RA. Cardiovascular responses to static exercise (isometrics anyone?). *Circulation.* 1970;41:172–173.

24. Driscoll EJ, Smilack ZH, Lightbody PM, Fiorucci RD. Sedation with intravenous diazepam. *J Oral Surg.* 1972;30: 332–343.

25. Vanderheyden PJ, Williams RA, Sims TN. Assessment of ST segment depression in patients with cardiac disease after local anaesthesia. *J Am Dent Assoc.* 1989;119:407–412.

26. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24-hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol.* 1977;39:390–395.

27. Roelandt J, Hugenholtz PG. Sudden death: prediction and prevention. *Eur Heart J.* 1986;7:169–180.

28. Armstrong WF, Jordan JW, Morris SN, McHenry PL. Prevalence and magnitude of ST segment and T wave abnormalities in normal men during continuous ambulatory electrocardiography. *Am J Cardiol.* 1982;49:1638–1642.

29. Stern S, Tzivoni D, Stern Z. Diagnostic accuracy of ambulatory ECG monitoring with ischaemic heart disease. *Circulation.* 1975;52:1045–1049.

30. Lown B, Wolf M. Approach to sudden death from coronary heart disease. *Circulation.* 1971;44:130–142.

31. Roelandt J, Klootwijk P, Lubsen J, Janse J. Sudden death during long-term ambulatory monitoring. *Eur Heart J.* 1984;5:7–20.

32. Willich SN, Maclure M, Mittleman M, Arntz HR, Muller JE. Sudden cardiac death. Support for a role of triggering in causation. *Circulation.* 1993;87:1442–1450.

33. Barkin ME, Middleton RA. ECG monitoring of oral surgery patients receiving a local anesthetic. *J Oral Surg.* 1978; 36:779–780.

34. Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. In: Goodman Gilman A, Rall WT, Nies AS, Taylor P, eds. *The Pharmacological Basis of Therapeutics.* 8th ed. New York, NY: Pergamon Press; 1990:187–220.

35. Okada Y, Suzuki H, Ishiyama I. Fatal subarachnoid haemorrhage associated with dental local anaesthesia. *Aust Dent J.* 1989;34:323–325.

36. Jage J. Circulatory effects of vasoconstrictors combined with local anesthetics. *Anesth Pain Control Dent.* 1992;2: 81–86.

37. Bishop PT. Frequency of accidental intravascular injection of local anaesthetics in children. *Br Dent J.* 1983;154: 76–77.

38. Lilley JD, Russell C, Walker RO, Waterhouse JAH. Use and misuse of equipment for dental local analgesia. *J Dent.* 1978;6:133–146.

39. Yagiela JA. Local anaesthetics. In: Neidle EA, Yagiela JA, eds. *Pharmacology and Therapeutics for Dentistry.* 3rd ed. St Louis, Mo: The CV Mosby Co; 1989:230–248.

40. Beaglehole R. Cardiovascular diseases in developing countries. *Br Med J.* 1992;305:1170–1171.

41. Nuffield Report. Education and Training of Personnel Auxillary to Dentistry. London, England: The Nuffield Foundation; 1993.