

# **A systematic review of cardiovascular effects of epinephrine on cardiac compromised dental patients**

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## **Abstract**

Local anaesthetics containing epinephrine are considered relatively safe pharmacological agents and have been used in dental practice for over fifty years. However, the use of epinephrine in local anaesthetics in cardiac compromised patients during dental procedures has been controversial. The current clinical guidelines concerning cardiac compromised patients recommend a maximum of 0.04 mg of epinephrine during one appointment, and even lower doses have been advocated by experts. The purpose of this systematic review was to determine whether there is any existing evidence to demonstrate that adverse outcomes are associated with the use of epinephrine-containing local anaesthetic in cardiac compromised patients during dental procedures. Extensive searches identified thirty articles, six of which met the inclusion criteria. Use of epinephrine in stable cardiac compromised patients was associated with minor but non-significant increases in heart rate and systolic and diastolic blood pressure. No adverse effects were reported and no interactions were observed with patients taking prescription medication for diagnosed cardiac conditions. The current literature therefore does not support claims that local dental anaesthetic containing epinephrine likely results in adverse events in cardiac compromised patients. However, the accumulated body of evidence does support the current guidelines which state that a total dose of less than or equal to 0.04 mg of epinephrine during dental procedures in cardiac compromised patients is safe. Further studies are required as the quantity and quality of evidence of the literature available proved to be problematic in this analysis.

**MeSH Keywords:** Local anaesthetic, epinephrine, cardiovascular disease, dentistry

## Introduction

The use of vasoconstrictors in local anaesthesia (LA) is a standard practice during dental procedures. The combination of epinephrine and lidocaine is the most widely used vasoconstrictor and local anaesthetic preparation in Ontario and abroad<sup>1</sup>. Epinephrine vasoconstriction increases duration and depth of anesthesia, provides hemostasis, and decreases systemic toxicity of LA. Local anaesthesia with insufficient amounts of epinephrine has been shown to provide inadequate pain control and hemostasis<sup>2,3</sup>. Impaired pain control and hemostasis may lead to undesirable patient health outcomes.

The issue regarding the use of epinephrine in LA in patients with cardiovascular disease (CVD) has been controversial. The concern is that administration of epinephrine may further stress the cardiovascular system via activation of  $\alpha$  and  $\beta$  adrenergic receptors. This can result in cardiac events such as acute hypertensive crisis, myocardial infarction, and arrhythmia. Furthermore, patients on medication may experience significant drug-drug interactions with epinephrine. For example, non-selective  $\beta$ -blockers also block  $\beta_2$  receptors, thereby eliminating  $\beta_2$  vasodilatation activity while leaving  $\alpha_1$  vasoconstrictor activity intact. Unopposed  $\alpha_1$  vasoconstriction by epinephrine may cause a hypertensive crisis. The potential for serious effects of epinephrine has resulted in some authors suggesting the use of LA without epinephrine in patients with CVD<sup>4</sup>. Current scientific data is insufficient to adequately address this concern, and recommendations for the use of epinephrine in dental practice are not in full agreement<sup>3,5,6</sup>.

In 1955 the New York Heart Association recommended a maximal dose of 0.2 mg of epinephrine ( $\leq 11$  cartridges of 1:100,000 epinephrine) when used with LA in patients with CVD<sup>7</sup>. This recommendation however, was not specific to dentistry, and was formed based on extrapolations from results of epinephrine in healthy patients. In 1964, a Working Conference of the American Dental Association and the American Heart Association stated that the concentrations of vasoconstrictors used in LA are not contraindicated in patients with CVD<sup>8</sup>. More recently, Malamed<sup>5</sup> and Bennett<sup>9</sup> have

recommended a maximal dose of vasoconstrictor for patients with CVD to be no more than 0.04 mg of epinephrine at one appointment. Furthermore, Kaneko<sup>10</sup> recommended even lower levels (0.02 mg) for severe cases of CVD.

Despite the general acceptance of these recommendations by clinicians, these guidelines may not be fully supported by current scientific evidence. The reason being is that most studies to date have been conducted on young and healthy subjects<sup>11-13</sup>, and the current recommendations were made on based on the results from this population group that were then extrapolated to patients with CVD. These results do not apply to CVD patients since hemodynamic responses to epinephrine in healthy patients differ from that of cardiovascular diseased patients. Furthermore, hemodynamic changes in CVD patients may be appear exaggerated when directly compared to the changes in healthy patients. These factors may lead to an underestimation of the amount of epinephrine required.

Nevertheless, recent studies have attempted to include more relevant patient populations. A recent systematic review by Bader *et al*,<sup>14</sup> examined the effects of epinephrine in LA on hypertensive patients. When comparing hypertensive patients with healthy patients they found only small, non-significant increases in systolic and diastolic blood pressure with no adverse outcomes. By limiting the inclusion criteria to hypertensive patients the authors created a strong design for appropriate comparisons within the studies cited. Yet, this limit leads to results that may lack ecologic validity as patients who are at risk from the effects of epinephrine present at the dental office with variable cardiac anomalies.

The purpose of this systematic review is to determine whether there is evidence to demonstrate that adverse outcomes are associated with the use of epinephrine-containing LA in patients with CVD during dental procedures. Furthermore, we wish to specifically address this question in relation to the existing guidelines that limits the amount of LA provided in a single appointment to 0.04 mg<sup>5, 9</sup>.

Therefore our specific aim is to examine the evidence that support 1) total doses of epinephrine  $\leq 0.04$  mg are likely safe and 2) total doses greater than 0.04 mg are potentially harmful.

## **Materials and Methods**

A systematic review of past and current scientific literature was conducted to address the key question, “What is the evidence for adverse outcomes with the use of epinephrine-containing local anaesthetic in cardiac compromised patients during dental procedures?” As part of our search criteria, we have decided to search for studies that compared the effects of epinephrine within the cardiac compromised patient group only. Studies that compared these patients to healthy patients were excluded. This was done for two reasons: 1) the literature shows that compared to healthy patients, patients with cardiovascular disease show little or no cardiovascular effects when exposed to comparable levels of epinephrine in local anaesthetic<sup>14</sup>, and 2) the pathophysiology of cardiac compromised patients differ drastically from that of healthy patients. Consequently, tissue response to epinephrine, effective dose, and drug interactions may differ drastically as well. Given the reasons above, we believe that studies focusing solely on CVD patients are more suitable in answering our question. Thus, the studies that will be our ideal are randomized, double-blinded control trials comparing the effects of LA with or without epinephrine in CVD patients.

The literature search was conducted using the databases Ovid Medline, EMBASE, and International Pharmaceutical Abstracts (IPAB). The search strategy initially included 1) a basic search using the keywords ‘local anaesthesia’ and ‘epinephrine’ and ‘hypertension’, followed by 2) an advanced search using the keywords cardiac’ or ‘cardiovascular’ or ‘coronary’. These results were combined to capture all articles encompassing these two topics. A further advanced search using the keywords ‘dental’ or ‘dentistry’ or ‘dental procedure’ was performed to capture dental related articles. These articles were then combined with the initial search to capture all articles pertaining to

the research question. These papers were limited to English and human studies yielding a total of 30 articles (**Table 1**).

The identified articles were reviewed initially at the title-level followed by a review of the abstracts and finally the full text. The reviews and subsequent decision to include or exclude the articles were performed independently by 2 reviewers. Disagreements between reviewers were settled through discussion requiring unanimous agreement at final decision. Our inclusion criteria identified studies that included: 1) patients with CVD in the experimental and control group(s), 2) exposure(s) to known concentrations of epinephrine in LA administered via injections, 3) any invasive dental procedure such as extractions, restorations, and scaling, and 4) measurements of either adverse cardiac outcomes or risk indicators. We defined CVD patients as anyone who has a history of cardiovascular events such as hypertension, coronary artery disease, angina, arrhythmia, stroke, myocardial infarction, or bypass surgery. The measurements of adverse outcomes included reports of arrhythmia, angina, hypertensive crisis, syncope, and myocardial infarction. We also considered a wide range of risk indicators such as heart rate, blood pressure, stroke volume, ECG readings, and cardiovascular biomarkers. Reviews and case reports studies were excluded. No restrictions were placed on patient age, sex, and whether or not they were on medication.

Out of the thirty articles identified, ten were excluded at the title-level (**Figure 1**). Six of these were review articles, with the remaining four others discovered to be irrelevant to our topic of interest. Eleven articles were subsequently excluded at the abstract-level. Nine of these studies examined changes only in healthy, normotensive patients, one had no experimental group, and one was irrelevant to our topic of interest. Three articles were excluded at the full paper level. One paper was excluded at the full paper level because the main purpose of the study was to compare the effectiveness of 4% articaine with 2% lidocaine. In addition, the articaine solution contained 1:200,000 epinephrine while the lidocaine solution contained 1:100,000 epinephrine. Although the experiment was performed using

CVD patients, no control groups were provided. Therefore we concluded that there were too many confounders in this study to adequately assess whether or not the outcome was strictly due to the effects of epinephrine. The second study was excluded as it did not provide any values and did not report any statistical analyses. The last article was a review paper that had no abstract provided electronically and was excluded only after the article was located in the library archives.

The final six articles that met the inclusion criteria were critically appraised for their quality using a checklist to assess evidence of efficacy of therapy or prevention that was adapted from Fletcher *et al*,<sup>15</sup>. The assessment of the quality of the studies did not affect whether or not the studies were included or excluded. The assessment merely provided a factor for consideration when we assess the totality of evidence for our key question.

## Results

The systematic review of the literature identified 6 studies that met the inclusion criteria (**Table 2**)<sup>6, 16-20</sup>. These studies included a total of 188 patients with some form of cardiovascular disease. Although some heterogeneity was present in the specific definitions of CVD in the studies reviewed, all definitions were based on common clinical criteria and all patients were characterized as stable at the time of the study. The age range of all studies reviewed was from 20 to 80 years (mean age, 58) with 77.7% of the patient population being male. Two studies specifically mentioned that the subjects recruited continued to receive their prescribed cardiac medications before dental procedures including  $\beta$ -blocking agents, calcium channel antagonists, nitrates, antiplatelets and lipid-lowering agents<sup>16, 20</sup>.

Five studies directly examined the effects of epinephrine in LA<sup>6, 16-18, 20</sup>. Although the purpose of the remaining study was to compare cardiac rate-pressure product and pressure-rate quotient with Holter monitoring, the authors used a methodology that applied to our assessment of the effects of epinephrine on CVD patients<sup>19</sup>. Five studies used LA solution of 2% lidocaine, with total epinephrine dosage ranging from 0.018 to 0.072 mg<sup>6, 16, 18-20</sup>. The remaining study employed 2% and 3% mepivacaine,

with greater than 0.036 mg of epinephrine used in 25.9% of the experimental group<sup>17</sup>. The dental procedures performed in the studies included restorations (n=1), periodontal surgery (n=1), scaling (n=1), extractions (n=2). One study did not report the type of treatment.

The principal outcomes examined in these studies were heart rate and blood pressure changes. Only two studies demonstrated an increase in heart rate from baseline to the procedure in patients receiving epinephrine compared to the group without epinephrine (5 bpm and 2.5 bpm, respectively) while one study reported a greater increase in the group without epinephrine, the changes were not considered significant. Niwa *et al*,<sup>20</sup> measured heart rate at 0, 2, 5, and 10 minutes after the intraoral injection of lidocaine with epinephrine and demonstrated a statistically significant increase in heart rate at the time of the injection. Three studies noted an increase in the systolic and diastolic blood pressure from baseline with the administration of LA with epinephrine<sup>16, 17, 20</sup>. Interestingly, an increase in systolic and diastolic blood pressure was also observed in patients who did not receive epinephrine in these studies. These changes occurred at the time of injection<sup>20</sup>, 2 minutes following injection<sup>16</sup>, or 1 hr following injection<sup>17</sup>. However, there were no significant differences reported between those that received LA with epinephrine and those that received LA alone<sup>16, 17, 20</sup>. In addition, to aid comparisons between studies, when not provided in the individual reports the mean arterial pressure (MAP) was calculated from changes in systolic and diastolic blood pressure by one of the review authors and recorded in **Table 2**. There were no significant differences in mean arterial pressure (MAP) from baseline values in any of the studies reviewed whether procedures were performed using local anaesthetic with or without epinephrine. However, a trend was observed where the maximum MAP occurred in conjunction with the administration of LA in two of the five studies<sup>17, 20</sup>. These readings were reported immediately or 2 min following administration of LA and MAP was observed to return to baseline by 5 minutes or following the dental procedure, respectively.

Heart rate and blood pressure changes were consistently measured by all six studies, but various additional outcomes were included as well. One study noted ST-segment depressions  $\geq 1$  mm from baseline in thirteen patients. However, these changes were noted in both the patients receiving LA with epinephrine and the patients receiving plain LA. Furthermore, these increases occurred either at the time of injection or two hours post-treatment, with no increase of other indicators of myocardial ischemia<sup>16, 17</sup>. In another study, plasma epinephrine was significantly elevated following anaesthesia with lidocaine and epinephrine, but did not show changes in heart rate and MAP<sup>6</sup>. Although not reported in the evidence table, one study analyzed for biochemical markers of myonecrosis (CKMB activity, CKMB mass and troponin T) and reported no differences amongst epinephrine and control groups up to 48 hours post-injection<sup>17</sup>. None of the studies reviewed had patient-reported adverse cardiac events such as chest pain, palpitation or diaphoresis.

## Discussion

The use of epinephrine in patients with CVD remains controversial. Epinephrine possesses adrenergic activity and can increase heart rate and blood pressure leading to adverse cardiac events. For example, Abraham-Inpijn *et al*,<sup>21</sup> found that patients with hypertension undergoing dental extractions had a greater increase in blood pressure than did normotensive patients after injection of 2% lidocaine with 1:80,000 epinephrine. In addition, significant arrhythmias also developed in 7.5% of the hypertensive patients. Recently, Malamed<sup>5</sup>, Bennet<sup>9</sup>, and recently Budentz<sup>22</sup> have recommended the maximum dose of 0.04 mg of epinephrine to be used in one dental session on patients with severe CVD. However, their recommendation failed to properly define “severe” CVD patients. In addition, the recommendations are based on expert opinion, case reports, and extrapolation from healthy patients.

In our analysis, we have shown that administration of epinephrine ranging from 0.018 to 0.072 mg are well tolerated by patients with CVD and did not produce any clinical indicators of adverse cardiac

outcomes. Two studies found no difference in heart rate, blood pressure, ST-segment depression, and arrhythmias between patients with coronary artery disease receiving up to 0.036 mg epinephrine and the control group. One study showed that despite significant elevation of plasma epinephrine after injection of up to 0.072 mg epinephrine, there was no significant rise in blood pressure and heart rate. In contrast, one study reported a significant increase in systolic blood pressure, heart rate, and stroke volume immediately after injection of 0.022 mg epinephrine. However, MAP remained unchanged and no cardiac symptoms were reported.

Given this evidence, administration of exogenous epinephrine in LA does not appear to cause significant hemodynamic changes in patients with CVD. Any transient increases in heart rate, blood pressure or arrhythmias were likely due to the release of endogenous catecholamines as a result of emotional stress or pain rather than the pharmacological effect of exogenous epinephrine. This is because peak exogenous epinephrine has been shown to occur five to eight minutes after injection<sup>23</sup>, whereas the hemodynamic changes were observed during or immediately after injection. Furthermore, the transient arrhythmias and ST-segment depressions that were observed occurred two hours post-injection. Conrado *et al*,<sup>17</sup> reported a significant increase in ejection fraction in patients given epinephrine. The authors argued that had there been an ischemic episode induced by exogenous epinephrine, ejection fraction should have decreased instead. This suggests that the use of epinephrine was unlikely to cause adverse cardiovascular outcome<sup>24</sup>.

Limiting anxiety and pain instead of exogenous epinephrine during dental procedure may be of greater importance when managing CVD patients, since both anxiety and pain result in a significantly increased release of endogenous catecholamines that can potentially lead to adverse cardiac effects<sup>25, 26</sup>. The release of catecholamines due to ineffective pain control during dental treatment have been noted to exceed that of exogenous administration from the use of LA with vasoconstrictors<sup>13, 14, 27, 28</sup>. Thus to gain effective pain control, administering adequate amounts of LA with vasoconstrictors in order to

prolong the duration of anaesthesia may in fact work in favour to the CVD patient. Interestingly, Niwa *et al*,<sup>20</sup> reported a diminished effect of epinephrine in patients with severe CVD and suggested that it may be due to alterations in the expression or function of  $\beta_1$  receptors. If that is the case, injection of exogenous epinephrine may not have as great an impact on cardiac function as would be expected in a patient with less severe CVD disease and a greater complement of functional receptors.

The main limitations of this review include 1) the heterogeneity of “cardiovascular disease” in our population selection, 2) the lack of studies describing or controlling for the effects of epinephrine on patients taking medications for the control of their heart disease, and 3) the lack of a power analysis in all of our selected studies.

The heterogeneity of our population group was due to the limited amount of evidence that is currently available with respect to the effects of epinephrine in CVD patients. Limiting our search to one type of heart disease at this point may not produce enough evidence for a proper analysis. The same reason applies to the medications controlling for heart disease, as there is simply very little studies at this point that take medication into account.

Nonetheless, the studies performed by Neves *et al*,<sup>20</sup> and Conrado *et al*,<sup>17</sup> have provided a basis for further research. Past studies investigating the effects of epinephrine-containing LA in CVD patients consisted mainly of observational studies utilizing healthy patients. These newer studies have used CVD patients in both the test and control groups and included patients that may or may not be on medication. We believe these studies realistically reflect a significant portion of the population that present at a dental office. More studies are needed of this nature, as well as studies that begin to cautiously and ethically test doses of epinephrine that exceed the 0.04 mg recommendation. Formal experiments demonstrating no adverse effects in cardiac compromised patients when exceeding 0.04 mg are required to set evidence-based safety limits of epinephrine administration.

Our findings suggest that there is no evidence demonstrating adverse events in patients with CVD when injected with epinephrine containing LA at doses of 0.04 mg or less during dental procedures. Our analysis supports the current guidelines suggesting  $\leq 0.04$  mg of epinephrine is likely a safe dose to use in cardiac compromised patients. Also, the evidence supports the recommendation that the current guidelines may be subject to change pending further research using doses exceeding 0.04 mg of epinephrine. To the dentist faced with a clinical decision to make in regards to a cardiovascular diseased patient who presents with pain during a procedure, we suggest that it may be in the patient's best interest to cautiously exceed the recommended dose as optimal pain control is important in the dental management of cardiac compromised patients. Further research is needed to re-evaluate the guidelines that are being practiced in today's dental clinics. With this in mind a, thorough medical history, along with evidence based knowledge will endow dentist to make the best clinical decisions.

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## References

1. Haas D, Lennon D. Local anesthetic use by dentists in Ontario. *J Can Dent Assoc* 1995;61(4):297-304.
2. Knoll-Kohler E, Knoller M, Brandt K, Becker J. Cardiohemodynamic and serum catecholamine response to surgical removal of impacted mandibular third molars under local anesthesia: a randomized double-blind parallel group and crossover study. *J Oral Maxillofac Surg* 1991;49(9):957-62.
3. Knoll-Kohler E, Fortsch G. Pulpal anesthesia dependent on epinephrine dose in 2% lidocaine. A randomized controlled double-blind crossover study. *Oral Surg Oral Med Oral Pathol* 1992;73(5):537-40.
4. Leviner E, Tzukert A, Mosseri M, Fisher D, Yossipovitch O, Pisanty S ea. Perioperative hemodynamic changes in ischemic heart disease patients undergoing dental treatment. *Spec Care Dentist* 1992;12(2):84-8.
5. Malamed S. Conscious sedation and general anesthesia techniques and drugs used in dentistry. *Anesth Prog* 1986;33(4):176-78.
6. Davenport R, Porcelli R, Iacono V, Bonura C, Mallis G, Baer P. Effects of anesthetics containing epinephrine on catecholamine levels during periodontal surgery. *J Periodontol* 1990;61(9):553-8.
7. New York Heart Association. Use of epinephrine in connection with procaine in dental procedures. *J Am Dent Assoc* 1955;50:108.
8. Working Conference of American Dental Association and American Heart Association on Management of Dental Problems in Patients with Cardiovascular Disease. *J Am Dent Assoc* 1964;68:333-42.
9. Bennett C. Monheim's local anesthesia and pain control in dental practice. 7 th ed. St Louis: Mosby-Year Book; 1984. 1984.
10. Kaneko Y. Management of cardiovascular patients in the dental office. *J Jap Dent Sci Assoc* 1990;9:3-18.
11. Meechan JG. Plasma potassium changes in hypertensive patients undergoing oral surgery with local anesthetics containing epinephrine. *Anesth Prog* 1997;44(3):106-9.
12. Miura K, Matsumura K, Nakamura Y, Kurokawa H, Kajiyama M, Takata Y. Suppression of cardiac sympathetic nervous system during dental surgery in hypertensive patients. *Hypertens Res* 2000;23(3):207-12.
13. Meyer FU. Hemodynamic changes of local dental anesthesia in normotensive and hypertensive subjects. *Int J Clin Pharmacol Ther Toxicol* 1986;24(9):477-81.
14. Bader JD, Bonito AJ, Shugars DA. A systematic review of cardiovascular effects of epinephrine on hypertensive dental patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;93(6):647-53.
15. Fletcher R, Fletcher S, Wagner E. *Clinical epidemiology - the essentials*. 3rd ed. 1996.
16. Neves R, Neves I, Giorgi D, Grupi C, Cesar L, Hueb W, et al. Effects of epinephrine in local dental anesthesia in patients with coronary artery disease. *Arq Bras Cardiol* 2007;88(5):545-51.
17. Conrado V, de Andrade J, de Angelis G, de Andrade A, Timerman L, Andrade M, et al. Cardiovascular effects of local anesthesia with vasoconstrictor during dental extraction in coronary patients. *Arq Bras Cardiol* 2007;88(5):446-52.
18. Vanderheyden P, Williams R, Sims T. Assessment of ST segment depression in patients with cardiac disease after local anesthesia. *J Am Dent Assoc* 1989;119(3):407-12.

19. Campbell R, Langston W, Ross G. A comparison of cardiac rate-pressure product and pressure-rate quotient with Holter monitoring in patients with hypertension and cardiovascular disease: a follow-up report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:125-8.
20. Niwa H, Sugimura M, Satoh Y, Tanimoto A. Cardiovascular response to epinephrine-containing local anesthesia in patients with cardiovascular disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;92(6):610-16.
21. Abraham-Inpijn L, Borgmeijer-Hoelen A, Gortzak RA. Changes in blood pressure, heart rate, and electrocardiogram during dental treatment with use of local anesthesia. *J Am Dent Assoc* 1988;116(4):531-6.
22. Budentz A. Local anesthetics and medically complex patients. *J Calif Dent Assoc* 2000;28:611-9.
23. Lipp M, Dick W, Daublander M, Fuder H, Stanton-Hicks M. Exogenous and endogenous plasma levels of epinephrine during dental treatment under local anesthesia. *Reg Anesth* 1993;18(1):6-12.
24. Pallasch T. Vasoconstrictors and the heart. *J Calif Dent Assoc* 1998;26(9):668-73, 76.
25. Goldstein DS, Spanarkel M, Pitterman A, Toltzis R, Gratz E, Epstein S, et al. Circulatory control mechanisms in vasodepressor syncope. *Am Heart J* 1982;104(5 Pt 1):1071-5.
26. Holroyd SV, Watts DT, Welch JT. The use of epinephrine in local anesthetics for dental patients with cardiovascular disease: a review of the literature. *J Oral Surg Anesth Hosp Dent Serv* 1960;18:492-503.
27. Meyer FU. Haemodynamic changes under emotional stress following a minor surgical procedure under local anaesthesia. *Int J Oral Maxillofac Surg* 1987;16(6):688-94.
28. Malamed SF. The periodontal ligament (PDL) injection: an alternative to inferior alveolar nerve block. *Oral Surg Oral Med Oral Pathol* 1982;53(2):117-21.

## Legend

**Figure 1.** A diagram representing the process by which the six articles analyzed in our review were selected.

**Table 1.** Summary of the search strategy performed and the resulting number of articles.

**Table 2.** Outcome measures for the six included studies.

# Resulting Articles

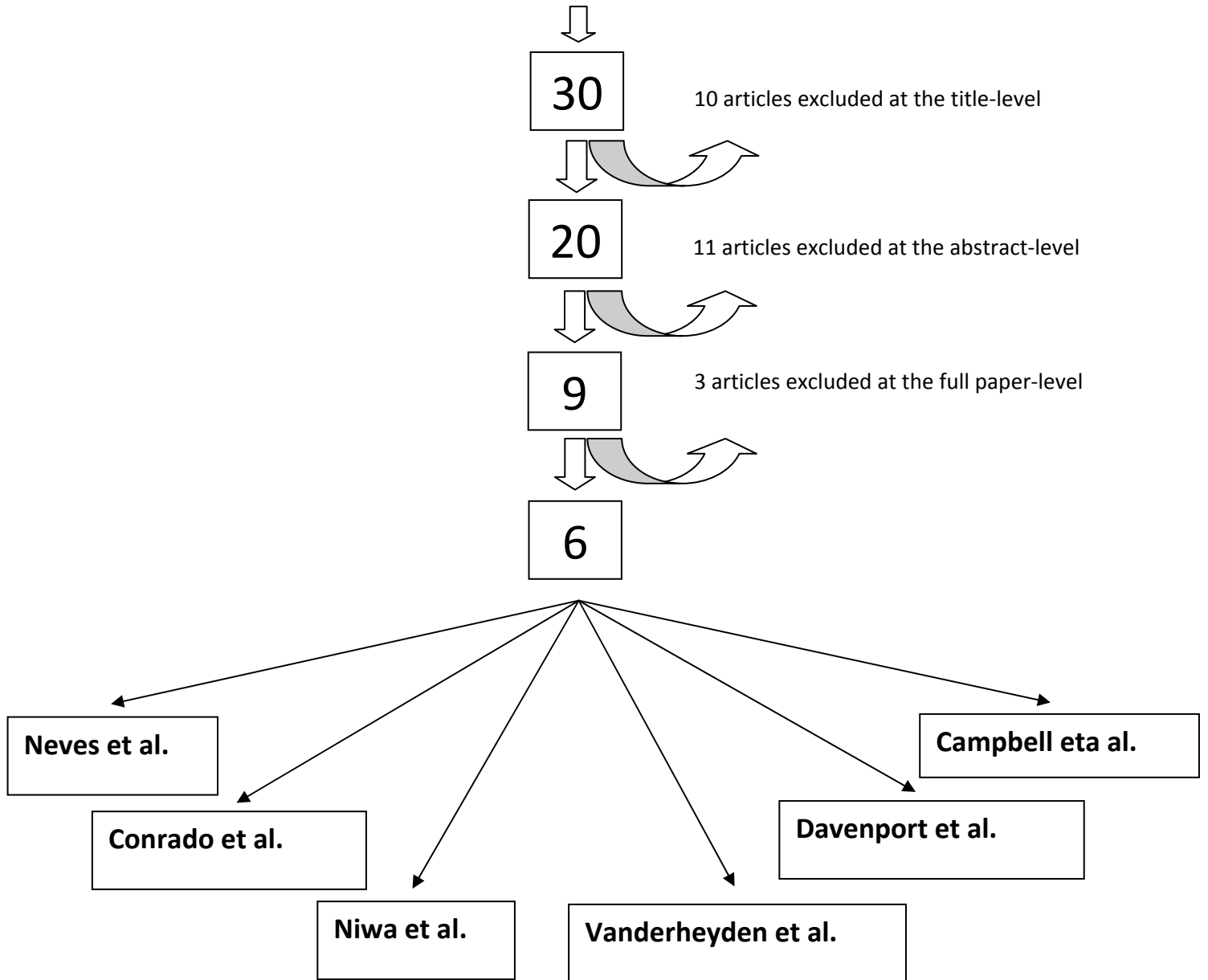


Figure 1

Search Parameter*	Resulting Articles
1) A <i>basic</i> search using the phrase 'local anesthesia epinephrine hypertension'	459
2) an <i>advanced</i> search of 'cardiac <b>OR</b> cardiovascular <b>OR</b> coronary'	907215
3) Combined 1 <b>AND</b> 2	106
4) an <i>advanced</i> search of 'dental <b>OR</b> dentistry'	184006
5) Combined 3 <b>AND</b> 4	30
*All search parameters were limited to human studies and in the English language	

**Table 1**

Authors	Group Criteria	Type of Treatment	Experimental Group	Main Outcome Measures			Additional Outcome Measures	Statistical Summary	Epi (mg)	LE
				Change in HR	Change in MAP					
Neves <i>et al</i> , 2007 <sup>16</sup>	a) CAD (≥70% luminal stenosis) b) EST positive for myocardial ischemia (< 3 months) c) absence of recent AMI	Restoration - single Md molar, premolar or canine	Lid, Epi n=30  Lid, nEpi n=32	0@dt 5@pt 0@dt 3@pt	8.36@dt  7.8@dt	ST-sd = 4 CA -dt = 3 ST-sd = 6 CA -dt = 4	no sig diff in any outcome measures	0.018 (n=15) 0.036 (n=15)	I	
Conrado <i>et al</i> , 2007 <sup>17</sup>	a) CAD b) stable angina on exertion c) absence of recent AMI d) controlled hypertension e) absence of coronary disease, stroke, or heart failure (< 3 months)	Extractions (1 -3)	2 % Mep, Epi n=27  3% Mep, nEpi n=27	0@pi -4@pt 5.3@pi 0.23@pt	9.34@pi 5.0@pt 7.33@pi 5.67@pt	ST-sd = 3 cEF pi/tp =1.13/1.2 ST-sd = 0 cEF pi/pt =-0.27/-0.18	cEFpt sig diff	< 0.036 (n=24) ≥ 0.036 (n=3)	I	
Davenport <i>et al</i> , 1990 <sup>6</sup>	a) stable CVD b) controlled hypertension c) ≥ 6 months post MI d) absence of unstable angina or CHF	Quadrant of replaced flap surgery	Lid, Epi n=9  Lid, nEpi n=9	5@inj 6@8 min pi 5@60 min pi 0@inj 5@8 min pi -2@60 min pi	2@inj 1@8 min pi 5@1 hr pi 1@inj 6@8 min pi 7@ 1 hr pi	cPE@2min pi=307 cPE@1hr pi=91 cPE@2min pi=46 cPE@1hr pi=120	cPE sig diff	0.072 (n=9)	II-1	
Niwa <i>et al</i> , 2001 <sup>20</sup>	Stable CVD	NR	NYHA class 1-3, Epi n = 27	5.1@inj 1.6%@2min pi 1.8%@10min pi	1.0%@2min pi -1.9%@10min pi	cSV@2min pi = 13.4 cSV@10min pi = 5.3 cTPR@2min pi = -9.8 cTPR@10min pi = -8.1	HR@inj sig diff cTPR sig diff cSV sig diff	0.0225 (n=27)	II-2	
Vanderheyden <i>et al</i> , 1989 <sup>18</sup>	ischemic heart disease (≥70% luminal stenosis)	Scaling/root planning (Q1/Q4 or Q2/Q3)	Lid, Epi n=20	0.4@inj 0.2@dt 1.0@pt	1.14@inj 2.94@dt 0.0@pt		No sig diff	0.036 (n=19) 0.054 (n=1)	II-2	
Cambell <i>et al</i> , 1997 <sup>19</sup>	a) abnormal RPP and PRQ b) controlled hypertension, CVD c) absence of stroke history	extractions or elective preprosthetic surgery	Lid, Epi n=16	NR	NR	RPP > 12K = 41% PRQ<1= 7.1%	RRP sig PRQ sig	≤ 0.060 (n=NR)	II-3	

HR, heart rate; MAP, mean arterial pressure; epi, epinephrine: µg, micrograms; LE, level of evidence; CAD, coronary artery disease; EST, exercise stress test; AMI, acute myocardial infarction; Md, mandibular; Lid, lidocaine; nEpi, no epinephrine; dt, during treatment; pt, post treatment; ST-sd, ST-segment depression; CA, cardiac arrhythmias; sig diff, significant difference; CVD, cardiovascular disease; MI, myocardial infarction; CHF, congestive heart failure; pi, post-injection; cPE, change in plasma epinephrine; Q, quadrant; inj, injection; Mep, mepivacaine; nMep, no mepivacaine; cEF, change in ejection fraction; NR, not reported; NYHA, New York Heart Association; cSV, change in stroke volume; cTPR, change in total peripheral pressure; RPP, Rate-pressure product; PRQ, pressure-rate quotient

**Table 2**

