Pulpal Inflammation and Incidence of Coronary Heart Disease

Kaumudi J. Joshipura, ScD,*†‡ Waranuch Pitiphat, ScD,*†§ Hsin-Chia Hung, ScD,†¶ Walter C. Willett, DrPH,†¶# Graham A. Colditz, ScD,†¶* and Chester W. Douglass, PhD*†

Abstract
Pulpal inflammation is primarily caused by coronal caries, and leads to root canal therapy (RCT). Chronic inflammation has been associated with various cardiovascular diseases. This study evaluates the association between pulp inflammation (using RCT as a surrogate) and incident coronary heart disease (CHD). We report results among males from the Health Professionals’ Follow-Up Study (HPFS), excluding participants with prior cardiovascular disease or diabetes. We obtained RCT data from the HPFS cohort (n = 34,683). Compared to men without RCT, those with ≥1 RCT had a multivariate RR of 1.21 (95% CI 1.05-1.40) for CHD. The association was limited to dentists (RR = 1.38; 95% CI 1.14-1.67). There was no association among nondentists (RR = 1.03). Dental caries was not associated with CHD. The results suggest a possible modest association between pulpal inflammation and CHD. (J Endod 2006;32:99-103)

Key Words
Cardiovascular disease, caries, epidemiology, inflammation, root canals

Dental infections have been associated with cardiovascular disease. Several studies have also shown associations between tooth loss and coronary heart disease (CHD) (1, 2) but we do not know the mechanisms or whether these associations are causal. Although antecedent periodontal disease may be a possible explanation, the data suggest that the association between tooth loss and CHD cannot be completely explained by periodontal disease (3). Antecedent dental caries and endodontic inflammation may also possibly contribute to the associations. Although some studies have found associations between a composite measure of oral health (including dental caries, periapical lesions, missing teeth, and periodontal disease) and cardiovascular disease (4, 5), very few studies have evaluated advanced dental caries or pulpal inflammation/root canal therapy (RCT) separately.

The study by Grau (5), a small case-control study, showed a multivariate odds ratio (OR) of 2.60 (95% CI: 1.2-5.7) between a composite dental disease index and stroke. When the composite index was broken up into individual components, stroke patients were more likely to have peri-apical lesions (p = 0.03 without controlling for confounders). There was no association between carious teeth or nonvital teeth and ischemic stroke. Another study by Jansson (6) suggested that the number of peri-apical lesions and number of carious surfaces were significantly associated with cardiovascular death. A recent cross-sectional study among 1056 women in Sweden (7) showed a significant crude association between number of RCT teeth (2 or more vs 0) and CHD. However, the associations were not significant in a multivariate model that included CHD risk factors as well as number of teeth.

Pulpal inflammation is caused primarily by coronal caries. Pulpitis leads to a periapical inflammatory response, which in turn may lead to a systemic inflammatory response that may increase CHD risk. RCT attempts to eradicate the microorganisms in the root canal biomechanically (8) or with intracanal antimicrobial agents (9). RCT is an elective procedure for teeth with acute nonreversible pulpitis (pulpal inflammation) to prolong the life of the teeth; the alternative treatment is extraction. We are assuming that RCT is for the most part a direct result of and therefore an appropriate surrogate measure of pulpal inflammation.

In this report, we evaluate the association of dental caries and pulpal inflammation, using RCT as a surrogate, with incident CHD within a large cohort study of health professionals. We wanted to test the hypothesis that pulpal inflammation may lead to increased risk of CHD.

Materials and Methods
The population for this report included participants in the Health Professionals’ Follow-Up Study (HPFS). HPFS is an ongoing cohort study of male participants in the US that started in 1986, and included 51,529 male health professionals including dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists 40 to 75 yr old (10). Mailed questionnaires to obtain information on medical history, health behaviors, and the occurrence of cardiovascular and other outcomes, were completed every 2 yr by the participants.
RCT and dental caries questions were added in the 1996 questionnaire that were mailed to the whole HPFS cohort. The specific questions asked in 1996 were:

1. How many of your permanent teeth ever had root canal therapy?
   Responses were: 0, 1, 2-4, 5-9, and 10+
2. Indicate years of all occurrences: Before 1976, 1976-86, 1987-90, 1991 or later. Similar questions were also asked replacing root canal therapy with a cavity.

The RCT exposure variable was time-dependent, and individuals may change their RCT status over time. For example, someone who had no RCT between 1976 and 1986 would have been assigned to the un-exposed group to predict the risk of developing CHD in 1987 through 1990. He would have been assigned to the exposed group in 1987 through 1990, to predict the risk of CHD in 1991 through 1996, if he had RCT in 1987 through 1990. Because RCT or caries before 1976 may likely be too distant in the past to be able to impact CHD incidence, and preliminary analyses confirmed this, the remaining analysis focused on occurrences between 1976 and 1996. For the primary analyses, we categorized RCT as none, or one or more root canals between 1976 and 1996. Because the majority of men had had 10 or more carious lesions, we categorized caries as 10+ or <10 teeth with caries history. Only participants who reported at least one carious lesion after 1976 were considered positive for caries.

Of the 43,233 participants who responded to the 1996 questionnaire, we included 43,058 participants who responded to the RCT and caries questions. We excluded 7,294 participants who reported myocardial infarction, stroke, revascularization procedures or diabetes before the follow-up and 1,081 participants who did not provide information on time periods for RCT from the analyses. Our final sample consisted of 34,683 participants who were included in the analyses.

Assessment of Endpoints

The primary endpoint for this study was incident CHD combining documented nonfatal myocardial infarction and fatal coronary disease, which have similar etiologies. We followed 34,683 eligible men and assessed incidence of CHD from 1986 to 2000. We reviewed the medical records for all participants who reported incident CHD. Records were reviewed by physicians who were unaware of the participants’ dental status.

Myocardial infarction was confirmed using World Health Organization criteria: symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzymes (11). Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable. The follow-up rate for nonfatal events was 97%. The fraction of self-reported cardiovascular events ultimately not confirmed by medical records or history was excluded from our case definition.

Deaths were identified from state vital records and the National Death Index or reported by next of kin, co-workers, and the postal system. Follow-up for the deaths was over 98% complete. Death certificates along with medical records were used to ascertain cause of death. Fatal coronary disease was defined as definite: (a) if it was confirmed from a hospital record or autopsy, or (b) if coronary disease was listed as the cause of death on the certificate and this was the underlying and most plausible cause, and evidence of previous coronary disease was available. If no medical records were available, we designated as probable CHD those cases in which CHD was the underlying cause on the death certificate. We also included as cases, sudden death within 1 hour of onset of symptoms with no plausible cause other than coronary disease. Among the total CHD cases, 33% were fatal. However, we only included those fatal cases that occurred after the 1996 questionnaire in our study.

Data Analyses

We documented 1,275 incident cases of CHD among eligible men who were free of CVD at baseline in 1986 when the study started. We evaluated the association between RCT and subsequent incident CHD: RCT from 1976 through 1986 was used to predict cases between 1987 and 1990; RCT from 1987 to 1990 was used to predict cases between 1991 and 1996; RCT from 1991 and 1996 was used to predict cases between 1997 and 2000. We also conducted analyses limited to recent or distant RCT, to assess the induction period. When we evaluated the number of RCT, we used RCT up to 1996 to predict cases in 1997 to 2000, because the number of teeth with RCT was assessed in 1996. We used Cox proportional hazards models to estimate relative risks (RR, incidence rate ratios) and 95% confidence intervals for the analysis. Caries was assessed as a binary measure comparing those with 10 or more teeth with history of caries to fewer than 10 carious teeth. We also evaluated a composite measure combining people with one or more RCT or 10 or more carious teeth compared to those with no RCT and less than 10 carious teeth. Total person-years of follow-up was calculated by summing the follow-up periods contributed by each participant, from the date of returning the 1986 questionnaire up to death, incidence of CHD, or January, 31, 2000.

Analyses limited to confirmed cases yielded similar results to analyses including confirmed and probable cases, although with less precision. Hence, we only present analyses that included both probable and confirmed cases. Each participant contributed only one end-point and the cohort at risk for each follow-up period included only those who remained free from reported incident CHD at the beginning of each follow-up period. Analyses were adjusted for age, smoking, alcohol, family history of myocardial infarction (MI), body mass index, physical activity, multivitamin supplement use, vitamin E use, aspirin use, reported hypertension, and hypercholesterolemia. These factors were updated for each follow-up period. In additional analyses, we controlled for the baseline number of teeth, and incident tooth loss.

We conducted subgroup analyses by age group, smoking status, baseline number of teeth and incident tooth loss during follow-up. We also evaluated the association separately among dentists and nondentists.

**Results**

Table 1 shows the distribution of age and various age-standardized potential CVD risk factors for participants with and without RCT. Participants with RCT tend to have more carious teeth. A smaller proportion of participants with RCT had fewer than 11 teeth at baseline, but participants with RCT tend to lose more teeth during follow-up than participants without RCT. Men with RCT have slightly less favorable CVD risk profiles; they are older, and slightly more likely to be current smokers.

Table 2 shows the relation between RCT, caries, and CHD. When we evaluated RCT between 1976 to 1996 as a risk factor for subsequent CHD, the association was significant in the analysis adjusting for age, smoking, and family history of MI (RR = 1.25; 95% CI = 1.08-1.44), and remained significant in the multivariate analyses (RR = 1.21; 95% CI = 1.05-1.40). The association became slightly stronger when we excluded men with only one RCT, hence, comparing men with two or more RCT to men with 0 RCT (multivariate RR = 1.24; 95% CI = 1.04-1.47). The associations were weaker and of borderline significance when we limited both these analyses (with and without excluding men with only one RCT) to RCT between 1987 and 1996, and subsequent CHD; multivariate RR = 1.17 and 1.19, respectively. The associ-
Table 1. Description of selected age-standardized risk factors in 1986 for CHD by history of RCT in 1976-1996

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>22189</th>
<th>12494</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.1 ± 9.2</td>
<td>54.2 ± 9.1</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>8.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Family history of MI (%)</td>
<td>12.4</td>
<td>12.5</td>
</tr>
<tr>
<td>Physical activity (MET-hr**/wk)</td>
<td>22.5 ± 35.1</td>
<td>22.1 ± 33.7</td>
</tr>
<tr>
<td>Obesity: Body Mass Index (kg/m2)</td>
<td>24.8 ± 5.5</td>
<td>25.0 ± 5.2</td>
</tr>
</tbody>
</table>

Table 2. Association between RCT and dental caries with incidence of CHD

<table>
<thead>
<tr>
<th>Number of RCT or Carious Teeth</th>
<th>CHD Cases</th>
<th>Person-yr</th>
<th>Adjusted for Age, Smoking, Family History of MI</th>
<th>Multivariate¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 vs ≥1 RCT 1976-1996²</td>
<td>1275</td>
<td>468,016</td>
<td>1.25 (1.08-1.44)</td>
<td>1.21 (1.05-1.40)</td>
</tr>
<tr>
<td>0 vs ≥2 RCT 1976-1996</td>
<td>991</td>
<td>374,875</td>
<td>1.29 (1.09-1.52)</td>
<td>1.24 (1.04-1.47)</td>
</tr>
<tr>
<td>RCT before 1976</td>
<td>1275</td>
<td>468,016</td>
<td>1.03 (0.90-1.19)</td>
<td>1.03 (0.89-1.18)</td>
</tr>
<tr>
<td>0 vs ≥1 RCT 1987-1996³</td>
<td>994</td>
<td>330,239</td>
<td>1.22 (1.03-1.44)</td>
<td>1.17 (0.99-1.39)</td>
</tr>
<tr>
<td>0 vs ≥2 RCT 1987-1996</td>
<td>777</td>
<td>264,611</td>
<td>1.26 (1.03-1.53)</td>
<td>1.19 (0.98-1.45)</td>
</tr>
<tr>
<td>≥10 vs &lt;10 caries⁴</td>
<td>411</td>
<td>117,054</td>
<td>1.09 (0.90-1.34)</td>
<td>1.17 (0.95-1.43)</td>
</tr>
<tr>
<td>≥1 RCT or ≥10 caries⁵ vs 0 RCT and &lt;10 caries</td>
<td>390</td>
<td>112,118</td>
<td>1.15 (0.89-1.49)</td>
<td>1.16 (0.90-1.51)</td>
</tr>
</tbody>
</table>

1 Models adjusted for age (5-yr categories); smoking (never, former, current: 1-14, 15-24, >25 cigarettes/d); alcohol (7 categories); family history of myocardial infarction (MI, before age 60); body mass index (quintiles); physical activity (quintiles); multivitamin supplement use; vitamin E use; aspirin use; reported hypertension and hypercholesterolemia.
354,683 men and 1275 cases.
192,983 men and 994 cases (cases in 1990-2000). Recent RCT was classified as 1987-1996.
Only if positive if responded positively to RCT and caries between 1976 and 1996.

Discussion

Our measure of pulpal inflammation is based on self-reported RCT obtained from questionnaires. RCT could have been performed in response to a chronic or acute pulpal inflammation (which cannot be differentiated in our RCT measure). In an earlier publication (12), we have shown that first time patients in a dental clinic are well able to report the number of RCT in their mouth (Spearman correlation = 0.83 comparing number of RCT from self report and clinical examination). We expect the validity of RCT to be even higher in our population of health professionals. However, as mentioned earlier, some of the RCT may have been performed for reasons other than pulpal inflammation, such as apical periodontitis and in the case of preventive endodontics to prepare the teeth for crowns. We could not distinguish between acute and chronic inflammation. The proportion of RCT that may be related to apical periodontitis is not known, but is likely to be too small to affect CHD risk. Importantly, periodontitis was not related with CHD in this cohort (1). Although RCT may be validly reported, they may not always be related to pulpal inflammation, hence using RCT as a surrogate for...
pulpal inflammation may bias the actual association between pulp
inflammation and CHD towards the null.

We found a significant association between history of RCT and
incidence of CHD. Furthermore, the association was limited to the
dentists. One hypothesis for the stronger association among dentists
is that RCT may be a more valid measure of pulp and periapical inflammation
among dentists than among nondentists. That is, some root canals are
performed on teeth that do not have pulps, for example, preventive
endodontics in fixed prosthodontics cases before crown placement.
When the RCT is done for crown preparation, the RCT would not be an
indication of pulp or periapical inflammation. Perhaps dentists are
less likely to submit themselves to the root canal procedure when there
has been no pulp inflammation. Our a priori assumption that an RCT
is directly linked to pulp inflammation may less often be the case for
the nondentist participants in this study. Consequently, the link between
RCT and pulp inflammation, and hence, between RCT and incident
CHD is perhaps stronger among dentists than among the nondentists in
this study population, accounting for the stronger association with inci-
dence of CHD.

Alternative explanations for finding associations only among den-
tists could be: (a) compared to dentists, nondentists would be more
likely to have affected teeth extracted than saved with RCT, implying
more misclassification of RCT/inflammation among nondentists (i.e.
true cases of inflammation would not be noted among nondentists be-
cause the teeth wouldn’t have had RCT); (b) dentists are more aware of
the linkages between RCT and crowns or periodontal surgery; and (c)
dentists would more likely correctly classify RCT re-treatments as being
on the same tooth, whereas nondentists might think that re-treatments
were two different root canals on two different teeth. Our study included
only males, so we cannot directly generalize to females, but there is no
reason to expect that the results would be different for females.

One report from a representative sample in Florida showed that
the most common reported reasons for a dental visit in which endon-
dontic treatment was performed were toothache (40%) and infected tooth/
abscess (30%); these reasons are usually associated with the clinical
diagnosis of pulpsitis and acute apical periodontitis (13). Following RCT,
79% of the teeth that did not have advanced procedures such as apico-
ectomy, root amputation, and re-treatments, had permanent restora-
tions placed, including amalgam, resins, post and cores, and crowns.
The manuscript did not specifically report on the proportion of root
Canals performed in preparation for a crown since the analysis was
based on dental participants’ self-reported reasons for a dental visit,
rather than actual causes for RCT. This question concerning relative
frequency of different reasons for RCT needs further research.

Consistent with some previous studies (5, 6), we did not find an
association between dental caries and incident CHD in multivariate
analyses. Number of carious teeth was not associated with CHD. Possi-
ble reasons could include: (a) there is no biologic relationship; (b) our
question on caries did not distinguish between active caries and fillings
(i.e. caries in the distant past); and (c) only deep caries may have an
impact that would not be captured by the number of carious teeth. The
association between RCT and incidence of CHD that was found in only
one of the two groups assessed may a result of chance. However, the fact
that the association was present among the dentists, rather than the
nondentists, increases the biological plausibility as discussed above.
The dose response for number of RCT, the persistence of the association
within all subgroups among the dentists, and the lack of association with
caries also makes the association between RCT and incidence of CHD
among dentists, less likely to be a result of chance. It is also possible that
the association may be because of residual confounding by behavior
related factors such as diet and utilization of dental care. However, it is
unlikely that the residual confounding would result in an association
limited only to dentists.

Earlier studies showed associations between RCT and/or periapi-
cical lesions and CVD, but the associations were not significant in multi-
variate analyses (4, 5). These studies had lower power and only the
composite measures were significant in multivariate analyses, hence, it
is hard to know whether there was a real association between RCT and
CHD. Two recent abstracts by Caplan et al. showed elevated multivariate
relative risks relating RCT and CHD in the Atherosclerosis Risk In Com-
munities Study (14) and Veterans’ Administration Dental Longitudinal
Study (15), although the associations were small.

People with more RCT may have a greater number of teeth, which
may be protective against CHD, and could thus dilute the association
between RCT and CHD. Although RCT may be an alternative to extrac-
tions for individual teeth, our data show increased tooth loss among
people with RCT, rather than among people with no RCT. Another pro-
spective study also showed that 19% of the teeth with RCT were extracted
within a 48-month follow-up period (16). Also, the associations are not
substantially different between people with or without tooth loss, and
adjusting for tooth loss did not change the RR. Hence, number of teeth
do not seem to impact the associations.

It is possible that CHD could influence whether a person under-
goes RCT. However, our study design is prospective and excludes par-
ticipants with pre-existing CHD. Hence, the association observed is not
because of CHD affecting the likelihood of RCT.

The flora of root canals is complex with a multitude of diverse
bacteria (17), which are predominantly anaerobic (18). The chronic
infection and inflammation could potentially lead to a systemic inflam-
matory response similar to that postulated for periodontal disease, pos-
sibly leading to increased risk of systemic disease. There have been no
publications suggesting that RCT has any adverse systemic effects since

---

**Table 3. Sub-group analysis of the association between one or more root canal treated teeth and CHD**

<table>
<thead>
<tr>
<th></th>
<th>All Males</th>
<th>Dentists</th>
<th>Nondentists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.21 (1.05-1.40)</td>
<td>1.38 (1.14-1.67)</td>
<td>1.03 (0.83-1.29)</td>
</tr>
<tr>
<td>≥24 Teeth</td>
<td>1.19 (0.87-1.61)</td>
<td>1.54 (0.97-2.45)</td>
<td>1.00 (0.66-1.52)</td>
</tr>
<tr>
<td>&gt; 24 Teeth</td>
<td>1.22 (1.03-1.43)</td>
<td>1.34 (1.09-1.66)</td>
<td>1.05 (0.80-1.36)</td>
</tr>
<tr>
<td>Incidental tooth loss (–)</td>
<td>1.21 (1.01-1.44)</td>
<td>1.43 (1.15-1.79)</td>
<td>0.94 (0.71-1.26)</td>
</tr>
<tr>
<td>Incident tooth loss (+)</td>
<td>1.24 (0.96-1.61)</td>
<td>1.24 (0.86-1.80)</td>
<td>1.24 (0.86-1.79)</td>
</tr>
<tr>
<td>Baseline age ≤55</td>
<td>1.45 (1.04-2.02)</td>
<td>1.67 (1.07-2.61)</td>
<td>1.26 (0.76-2.08)</td>
</tr>
<tr>
<td>Baseline age &gt;55</td>
<td>1.17 (1.00-1.37)</td>
<td>1.33 (1.08-1.64)</td>
<td>0.99 (0.77-1.27)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.33 (0.89-1.97)</td>
<td>1.98 (1.19-3.32)</td>
<td>0.89 (0.48-1.68)</td>
</tr>
<tr>
<td>Past or never smokers</td>
<td>1.20 (1.02-1.40)</td>
<td>1.33 (1.08-1.63)</td>
<td>1.05 (0.83-1.33)</td>
</tr>
</tbody>
</table>

1Models adjusted for age (5-yr categories); smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes/d); alcohol (7 categories); family history of myocardial infarction (before age 60); body mass index (quintiles); physical activity (quintiles); multivitamin supplement use; vitamin E use; aspirin use; reported hypertension and hypercholesterolemia.
the dismissal of the focal infection theory of the early 1900s (19). RCT in our study is a surrogate for pulpal inflammation; we do not expect the RCT itself to lead to adverse systemic outcomes. Further research is needed to corroborate the association between pulpal inflammation and CHD in other populations, to assess whether the association is causal, and to evaluate pathways for this association.

In our study, RCT was associated with a small increased risk of incident CHD among men. The association was limited to dentists where the RCT is more likely to reflect pulpal inflammation as compared to nondental health professionals.

Acknowledgments

We are indebted to the participants of the Health Professionals Follow-Up Study for their continued cooperation and participation; to Karen Corsano, Mira Kaufman, and Al Wing for computer assistance; to Jill Arnold, Kerry Demers, Betsy Frost-Haues, and Mitzi Wolff for their assistance in the compilation of data.

This research was supported by grants DE12102, HL35464, and CA87969 from the National Institute of Health.

References