

Does Cervical Manipulative Therapy Cause Vertebral Artery Dissection and Stroke?

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Objective: Does cervical manipulative therapy (CMT) cause vertebral arterial dissection (VAD) and subsequent ischemic stroke? What is the best estimate of the incidence of CMT associated with VAD and ischemic stroke?

Methods: The questions were addressed with a structured evidence-based clinical neurologic practice review. Participants included neuroscience students, consultant neurologists, clinical epidemiologists, medical librarians, and clinical content experts. A critically appraised topic format was employed, starting with a clinical scenario and structured question. The participant group devised search strategies, located and compiled the best evidence, performed critical appraisals, synthesized the results, summarized the evidence, provided commentary, and declared bottom-line conclusions.

Results: The search yielded 169 citations, of which 55 were deemed most relevant. From this return, we selected 26 publications of the highest evidence available: 3 case-control studies, 8 prospective and retrospective case series studies, 4 illustrative case reports, 1 survey, 1 systematic review of observational research, 5 reviews, and 4 opinion and expert commentary pieces. Five of the applicable 7 criteria for causation were satisfactorily met and supported weak to moderate strength of evidence for causation between CMT and VAD and associated stroke, especially in young adults. Young vertebrobasilar artery territory stroke patients were 5 times more likely than controls to have had CMT within 1 week of the event date (OR 5.03, 95% CI, 1.32–43.87). No significant associations were found for those ≥ 45 years of age. The best available estimate of incidence is approximately 1.3 cases of VAD or occlusion

attributable to CMT for every 100,000 persons <45 years of age receiving CMT within 1 week of manipulative therapy.

Conclusions: Weak to moderately strong evidence exists to support causation between CMT and VAD and associated stroke. Ultimately, the acceptable level of risk associated with a therapeutic intervention like CMT must be balanced against evidence of therapeutic efficacy. Further research, employing prospective cohort study designs, is indicated to uncover both the benefits and the harms associated with CMT.

Key Words: vertebral artery dissection, cerebrovascular disorders, chiropractic manipulation, spinal manipulation, causality, incidence, critically appraised topic, evidence-based medicine

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Vertebral artery dissection (VAD) is considered rare, with an annual incidence of approximately 1 to 1.5 per 100,000 people.¹ Although VAD accounts for only 2% of ischemic stroke in the general population, it is responsible for nearly 20% of stroke in younger patients (<40 years).¹ Numerous healthcare professionals and scientists have postulated that the high incidence of VAD in this population group could be associated with an increase in the popularity of cervical manipulative therapy (CMT) among this age group.² CMT has been performed since the 18th century³ to treat symptoms of neck pain, muscle tension and migraine.⁴ An estimated 10 million patients visited a chiropractor between 1995 and 2005 for a total of 125 million visits.³ There has been significant discussion and debate about the association between VAD and CMT as a result of the high rate of CMT performed and the high incidence of VAD in this young population group.² The first case report that suggested an association between CMT and VAD was published in 1947 by Pratt-Thomas and Berger.⁵ A number of experts suggest that the swift thrusting movements that are used during cervical spine adjustments could subject the vertebral artery (VA) to dissection.⁴ The role of CMT in VAD with subsequent stroke remains ambiguous and a clear causal relationship has not yet been established in the health sciences community. Accordingly, the role of CMT remains a controversial topic that sparks debate and disagreement between neurologists and chiropractors. We sought to retrieve, collect,

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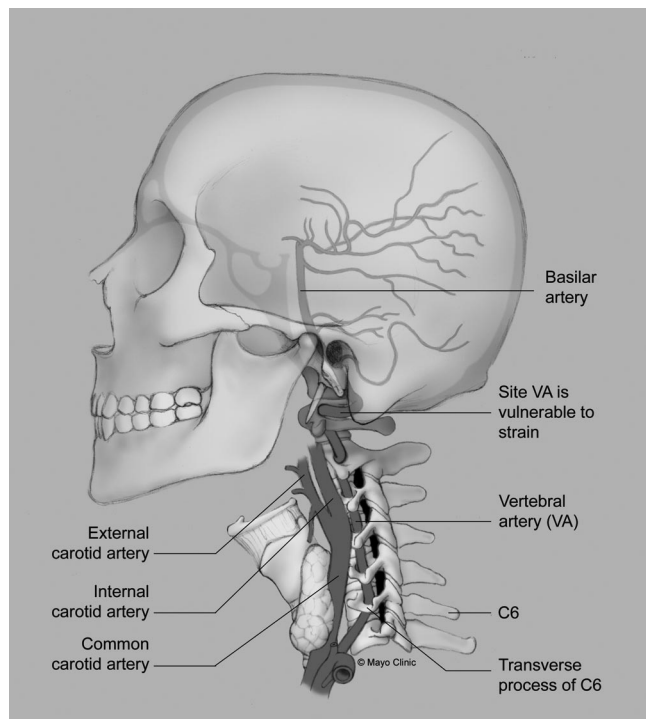


FIGURE 1. Right lateral view of the vertebral artery and carotid artery, highlighting where the vertebral artery is susceptible to dissection.

appraise and evaluate the available literature to determine the incidence of CMT associated with VAD and relative strength of evidence for or against a causal relationship between CMT and VAD.

ANATOMY AND PATHOPHYSIOLOGY

The VA can be divided into 4 segments⁶: 1) the VA arises from the first branch of the subclavian artery to the transverse foramina of C5 and C6; 2) from C5–C6 to C2, the VA is contained inside the transverse foramina; 3) at C2 the VA begins a tortuous course, running posterolaterally to loop around the posterior arch of C1 and passing between the atlas and occiput; 4) the VA then pierces the dura at the foramen magnum and continues to the junction of the pons and medulla, where it joins the proximal basilar trunk.

Figure 1 illustrates the anatomy of the VA. VAD occurs most often at the third and fourth segments of the VA. Arterial dissection can be described as either subintimal or subadventitial, depending on the proximity of the dissection to each layer of the artery.⁷ A subintimal dissection is a tear in the intima that separates the intima from the tunica media. This causes the lumen of the artery to narrow as normal blood flow causes blood to penetrate into the vessel wall. In addition, a subintimal dissection could form a primary intramural hemorrhage of the vasa vasorum⁸ that ruptures into the true lumen. When this subintimal hemorrhage ruptures into the true lumen distally, a double lumen can form, which is depicted in Figure 2.^{1,7} Subadventitial dissections occur at the

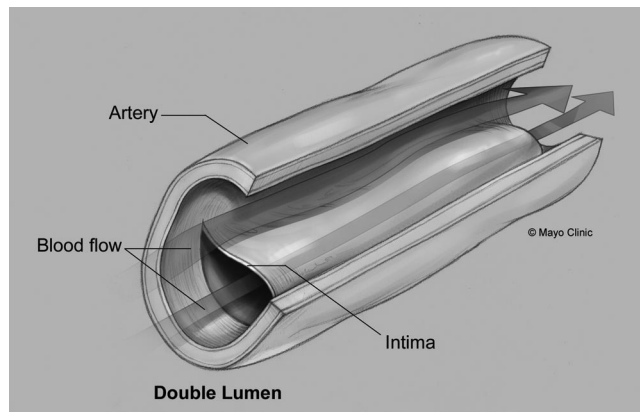


FIGURE 2. Formation of a double lumen caused by the rupture of a subintimal hemorrhage back into the lumen.

layer of the adventitia but still affect the intimal layer. Subadventitial dissections are often referred to as dissecting aneurysms or pseudoaneurysms because they can cause the artery to dilate. Regardless of the affected layer, the dissection can subsequently spread varying distances of the artery, usually in the direction of blood flow. Ischemic stroke can occur as a result of arterial dissection by a number of mechanisms. For example, the artery may become occluded near the site of the dissection or a fragment of thrombus may become dislodged and cause embolization distal to the dissection.⁷

CMT is generally accepted as the manual movement of cervical vertebrae beyond the normal range of motion.⁹ CMT is traditionally performed by chiropractors; however, it is often provided by orthopedic surgeons, physiotherapists, osteopaths, general practitioners, homeopaths, and neurologists.^{3,9} The specific technique of CMT that is employed by these healthcare professionals varies greatly. Such techniques include rotation of the cervical spine to the point of restriction, followed by high-velocity, low-amplitude thrust; flexion with a lateral to medial thrust in the absence of rotation; toggling, a shallow thrust, followed by quick withdrawal; instrument-assisted therapy to deliver specific thrusts; a drop table mechanism involving separate head, thoracic, lumbar and pelvic supports; and nonforce manipulation.¹⁰ “Short lever arm” describes a maneuver in which force is applied near the joint. If force is applied distant from the joint, the maneuver is termed “long lever arm.”⁹ The specific maneuver that is responsible for arterial dissection has not been adequately assessed and identified.¹¹ CMT has been used to treat neck pain and stiffness, muscle-tension headache, migraine, pain in the upper extremities, thoracic spine, lumbar spine, and lower extremities, vertigo, scintillations, nausea, paraesthesia, and other musculoskeletal pain.^{3,4,9,12,13}

Clinical Scenario

A 39-year-old healthy bus driver with lumbosacral degenerative disc disease was under the care of a chiropractor. Over the preceding year he had undergone 4 spinal manipulative treatment sessions with an emphasis on the lumbosacral region. The therapist suggested CMT to balance

the overall spine alignment. While the patient was undergoing CMT, he immediately developed new, moderately sharp, left posterior neck pain. He did not report these symptoms to his therapist and he departed the clinic with persistent aching left posterior neck pain. One hour and 45 minutes after the CMT session, he developed the acute onset of vertigo, disequilibrium, nausea, vomiting, dysarthria, dysphagia, and ataxia. He picked up a frozen pizza in his left hand and noticed loss of temperature sensation in his right hand when he transferred it from one hand to another. Upon presenting to the emergency department, he was discovered to have a left Horner syndrome, dysarthria, dysphagia, reduced right-sided pain and temperature sensation, left finger-to-nose and heel-to-shin dysmetria, and gait ataxia. Magnetic resonance imaging revealed increased diffusion weighted imaging signal change in the left lateral medulla and left cerebellar hemisphere consistent with an acute posterior inferior cerebellar artery territory infarction. Magnetic resonance angiography confirmed an acute C2 VAD. Naturally, the patient asked if the CMT to which he had just been exposed was the cause of his newly diagnosed VAD and resultant left lateral medullary and cerebellar infarction.

CLINICAL QUESTIONS

Does CMT cause VAD and subsequent ischemic stroke? What is the incidence of CMT associated with VAD and ischemic stroke?

Search Strategy

Ovid MEDLINE database was searched for the time period of 1950 to the second week of September 2007. The MeSH terms of manipulation, chiropractic and manipulation, and spinal were searched as well as a variety of synonymous textwords including cervical manipulative therapy, CMT, and chiropractic truncated. These terms were combined using the Boolean "OR" and yielded 5562 citations. In the same manner, another set was created using MeSH terms vertebral artery, vertebral artery dissection, and cerebrovascular accident and textwords vertebral artery dissection, vertebral artery injury and VA dissection. The result was 49,509 citations. The 2 subject sets were combined with the Boolean operator "AND." When limited to human and English, the yield was 169 citations. The Ovid Saved Search for Etiology (emphasizing comprehensive retrieval) that detects cohort studies, risk, odds ratio, relative risk or case controls was applied to the final set and resulted in 55 citations. Although these 55 citations detected a higher level of evidence, all 169 citations were reviewed. EMBASE and CINAHL (Cumulative Index to Nursing and Allied Health Literature) were also searched since CINAHL indexes a number of chiropractic journals. No additional articles of high quality evidence were detected in these databases. We selected the 26 highest levels of evidence publications: 3 case-control studies, 8 prospective and retrospective case series studies, 4 illustrative case reports, 1 survey, 1 systematic review of observational research, 5 reviews, and 4 opinion and expert commentary pieces.

EVIDENCE, RESULTS AND CRITICAL APPRAISAL: CAUSAL EFFECT OF CMT ON VAD

In clinical medicine one cannot prove or disprove causal relationships beyond any doubt. Accordingly, one can only increase or decrease his or her conviction of a cause-and-effect relationship by means of empiric evidence to the point at which, for all intents and purposes, cause is established or deemed implausible. A postulated cause-and-effect relationship must be fully examined by numerous methods.¹⁴ When considering a possible causal relationship, the strength and validity of the research design employed is an important piece of evidence in support of or against a causal relationship. Although randomized controlled trials are the highest form of evidence for establishing a cause-and-effect relationship, these studies are rarely feasible when exploring causes of diseases or conditions. Consequently, evidence for a cause-and-effect relationship becomes weaker as the research design deviates further from a randomized controlled trial since other designs do not adequately protect against possible biases. After randomized controlled trials, the next best designs are well-conducted prospective cohort studies, followed by case-control, cross-sectional, case series, case reports, surveys, and expert opinion and commentaries.

Sir Austin Bradford Hill developed a series of criteria for causation in 1965. These criteria are not all of equal weight; however, they are useful in deciding if a relationship is truly causal or mere association. We used Sir Bradford Hill's criteria for causation as well as the strength of the research designs to present and evaluate the evidence for or against a causal relationship between CMT and VAD.

Temporality: Does Cause Precede Effect?

In a retrospective case series by Reuter et al, 36 patients with VAD associated with CMT in Germany were studied over a 3-year period.³ No neck or head trauma prior to the administration of CMT was reported for any of the cases. CMT was solicited for multiple complaints including muscle tension and pain, tension headache, migraine, vertigo, lower back pain, scintillations, paraesthesia, and nausea. Regardless of the reason each patient sought CMT, focal deficits were readily noticed by the majority between the time CMT was administered and 48 hours thereafter. Five subjects (14%) experienced symptoms during the administration of CMT, 4 (12%) within 1 hour, 5 (14%) between 1 and 6 hours, 7 (20%) between 6 and 12 hours, 5 (14%) during the 12 to 48 hour time frame, and the remainder beyond the 48 hour point.

This study had several limitations, including a lack of control group and employment of a retrospective survey-derived case series design which is insufficient to establish causation.

Smith et al conducted a nested case-control study that compared patients with spontaneous cervical artery dissection to a control group of patients with stroke and transient ischemic attack (TIA) of similar age and sex to understand the role of CMT in the pathogenesis of dissection.⁸ These subjects with dissection were more likely to have had CMT within 30 days of the index stroke or TIA. Two subjects with VAD had stroke within seconds of CMT. The latency from

CMT to neurovascular event was statistically significantly shorter (mean 1.4 days) for patients with dissection than for the control group (mean 8.4 days).

Rothwell et al conducted a population-based nested case-control study to test the association between CMT and VAD. Adding to the compelling evidence of temporality, the results for those aged <45 years revealed VAD cases to be 5 times more likely than controls to have visited a chiropractor within 1 week of the VAD.² Haldeman et al performed a retrospective review of 64 medico-legal cases of stroke that were temporally associated with CMT. Forty (63%) patients reported immediate onset of neurologic symptoms following CMT. In 8 cases the onset was between 5 and 30 minutes, in 12 cases between 30 minutes and 48 hours, and in 3 cases between 48 hours and 11 days.¹⁰

Dziewas et al retrospectively studied a series of 126 consecutive patients with cervical artery dissection. CMT was performed significantly more often in patients with VAD (30%) than with carotid artery dissection (6%). The interval between CMT and the onset of neurologic symptoms ranged from several seconds to 10 days.¹ Hunfagel et al reported a case series of 10 patients with stroke following CMT, 8 of whom had VAD. Half of the patients reported the onset of neurologic symptoms immediately after the procedure and the other half reported onset within 2 days of CMT.¹³

Based on the available evidence, does CMT precede VAD? The overall answer is yes. The temporality criterion is satisfactorily met with weak to moderate strength of evidence for a causal effect between CMT and VAD.

Strength of Association: Is There a Large Relative Risk?

A strong association between a purported cause (eg, CMT) and an effect (eg, VAD) as expressed by a large relative risk, is stronger evidence for a causal relationship than a weak association. To determine a strong association with large relative risk, the most superior research design is a randomized controlled trial with adequate sample size, concealment of allocation, blinding, and complete follow-up. A well-conducted prospective cohort study is the next best design since it can minimize confounding, selection bias and measurement biases. Unfortunately, these study designs do not exist for the evaluation of CMT and VAD. Instead, we are required to rely upon observational research.

A systematic review of publications from 2001 to 2006 that evaluated the adverse effects of spinal manipulation failed to identify a single experimental prospective randomized or nonrandomized controlled clinical trial or an observational prospective cohort study.⁹ In place of these studies, the authors uncovered 3 case-control studies, 2 prospective case series, 4 retrospective case series, 3 surveys, and 32 case reports. These weaker observational study designs do not adequately protect against possible biases. Nonetheless, these publications constitute the best available evidence from which to draw conclusions regarding causality.

Rothwell et al consulted hospital records in Ontario, Canada from 1993 to 1998 to identify patients with vertebrobasilar artery territory stroke, secondary to dissections and occlusions of the arteries of the posterior circulation. Each of

the 582 cases was age and sex matched to 4 controls from the Ontario population with no history of stroke at the event date. Public health insurance billing records were used to document the use of chiropractic CMT services before the event date. The results showed that young patients (<45 years) with vertebrobasilar artery territory stroke were 5 times more likely than controls to have visited a chiropractor within 1 week of the event date (OR 5.03, 95% CI, 1.32–43.87).² No significant associations were found for those aged ≥45 years. Limitations of the study include, over- or under-inclusiveness of cases, inability to capture events in nonhospitalized patients, missing subarachnoid hemorrhages secondary to intracranial VAD, narrow definitions of vertebrobasilar stroke by ICD-9 codes, absence of validation of stroke diagnosis by appropriate neuroimaging, and possible incorrect categorization of chiropractor billing diagnostic codes. The study does not answer why an association between CMT and vertebrobasilar artery stroke was observed in the young adults only. We speculate that the older adult population is more likely to have vertebrobasilar artery stroke related to other predisposing medical conditions such as atherosclerosis, cardioembolism or small vessel disease; hence diluting the potential effect of CMT.

Smith et al used a nested case-control study design to review patients <60 years of age with cervical artery dissection (n = 151) and ischemic stroke or TIA from 1995 to 2000 at 2 university medical centers to determine if CMT is an independent risk factor for cervical arterial dissection. All patients were age and sex matched to controls (n = 306).⁸ The results revealed that VAD was independently associated with CMT within 30 days (OR 6.62; 95% CI, 1.4–30.0). Limitations include retrospective data collection from patients who responded to solicitation, potential for recall bias, no standardization of diagnostic work-up, and conceivable misclassification of VAD.

In a case-control study by Dittrich et al, 47 consecutive cervical artery dissection cases were compared with 47 similar age-matched controls with consecutive ischemic stroke due to etiologies other than arterial dissection. By standard face-to-face interviews, the event of multiple mechanical trigger factors such as lifting, sexual intercourse, neck trauma, jerky head movements, sports activity, and CMT prior to symptom onset was assessed. The results revealed no statistically significant association between any single mechanical risk factor and cervical arterial dissection. Although CMT was found to be more frequently associated with stroke due to cervical arterial dissection compared with stroke of other etiologies, this finding failed to reach statistical significance.¹⁵ However, the cumulative analysis of all mechanical trigger factors did reveal a significant association of dissection-related stroke compared with stroke of other causes ($P = 0.01$).

VAD and resultant ischemic strokes are rare events with potentially dire consequences. When an adverse event occurs in healthy young adults, one has a natural tendency to seek an explanation. In every case-control study, recall or rumination bias may result in exaggeration of the apparent association with CMT. Furthermore, the association between

CMT and VAD may also result from confounding. The situation of confounding could occur if, for example, a patient has neck pain due to arterial dissection of etiology other than CMT and the patient subsequently seeks CMT for the symptom of neck pain. In this case, it would be unclear to a clinician if dissection and stroke actually preceded or followed CMT. Without adoption of a more rigorous study design (eg, randomized controlled trial or cohort study), these potential sources of bias cannot be adequately addressed and avoided. Unfortunately, the prospective study of the rare event of VAD would be difficult, costly, and time consuming.

Is the association between CMT and VAD expressed by a large relative risk? The answer remains equivocal based on the evidence. The strength of association criterion is only partially met by observational studies of low to moderate validity that present moderately large estimates of association (OR 5–6). Accordingly, the net result of strength of association illustrates weak to moderate evidence for causality.

Dose-Response: Are Larger Exposures to Cause Associated With Higher Rates of Disease?

Reuter et al noted that 33% of the patients in their retrospective case series had multiple treatments of CMT without complications prior to the subsequent detection of VAD. This data reflects that VAD can occur after one or multiple CMT visits. Additionally, multiple visits without complications do not exclude the later occurrence of VAD.³ In a case-control study to test the association between CMT and VAD by Rothwell et al, a higher number of CMT visits was associated with higher rate ratios for the risk of VAD.² In a retrospective case series by Haldeman et al, only 14% of patients were exposed to a single treatment of CMT. Most of patients received CMT prior to the onset of cerebrovascular symptoms: 1 to 5 treatments in 16% of patients, 6 to 15 in 22%, 16 to 35 in 17%, 36 to 55 in 11%, 56 to 100 in 8%, and >100 in 3%. In the small case series by Hufnagel et al half of the patients were found to have undergone a single treatment of CMT. The other half had 2 to 10 CMT treatments before the diagnosis of VAD was made.¹³

Are larger exposures to CMT associated with higher rates or higher risk of VAD? In short, yes; one is at a higher risk for VAD and stroke with increasing exposure to CMT. The dose-response criterion is satisfactorily confirmed by moderately strong evidence for a cause-and-effect relationship between CMT and VAD.

Reversibility: Is Reduction in Exposure Associated With Lower Rates of Disease?

The reversibility criterion does not directly apply to our question of causation. While there is evidence to support that people who frequently receive CMT are at a higher risk of VAD, reversibility is not possible in the case of CMT. Once CMT has been performed and VAD with subsequent stroke has occurred, one cannot reverse, withdraw, or lessen the exposure to the hypothesized culprit of disease. Therefore, this causation criterion cannot be adequately satisfied.

Consistency of Association: Do Several Different Studies Come to the Same Conclusion?

Case reports confirm that a number of individuals who undergo CMT experience a VAD and ischemic stroke. The VAD that occurs is postulated to be due to intimal tearing most commonly at the level of the atlantoaxial joint due to overstretching the vertebral artery during rotational manipulation. Surveys reveal that VAD and ischemic stroke are recognized complications of CMT. Multiple retrospective case series confirm that CMT can be associated with VAD and ischemic stroke. Prospective case series help corroborate results from earlier studies. The majority of case control studies report that CMT is an independent risk factor for VAD and ischemic stroke. Although these studies collectively suggest that VAD and stroke are, indeed, associated with CMT, each study also highlights that it is challenging to make a causal inference.⁹

Do multiple studies come to the same conclusion about CMT associated with VAD and ischemic stroke? In conclusion, yes; multiple observational studies of different designs, with different patient populations, conducted at different times and in different settings demonstrate a consistent association between CMT and VAD. However, all authors have been cautious to suggest proof of causality. The consistency criterion is satisfied with evidence of weak strength for a causal relationship between CMT and VAD.

Biologic Plausibility: Is the Assertion of Cause and Effect Consistent With Our Knowledge of the Mechanisms of Disease?

The anatomy of the VA suggests that VAD as a result of CMT is plausible. As the third segment of the VA loops around the posterior arch of C1, it changes from a vertical path to a horizontal path and passes between the atlas and occiput.¹⁶ At this point, the VA could be most susceptible to dissection during CMT because the artery passes through a bony region that could compress the artery with rotation or tilting of the head and neck.^{2,8} At the University of Calgary, researchers directly measured how the forces anticipated during CMT are transmitted through the cervical skeletal and soft tissues to the vertebral arteries. In addition, the group explored how these forces compare with the limits of arterial integrity, which were assessed by deliberately stretching vertebral arteries that were excised from unembalmed, postmortem patients to the point of rupture. The investigators concluded that the values of force transmitted to the vertebral arteries during CMT were less than the forces recorded during normal range of motion (ie, normal turning of the neck).^{17–19} The results of this study may not reflect the in vivo scenario for several reasons. VAD associated with CMT most commonly occurs at the C1–C2 level, yet this study did not measure the forces in this location. Stretch by tensile forces may not reflect the type of artery deformation that is suspected to occur in patients that have undergone CMT. Moreover, one would expect that the range of motion of elderly patient cadavers to be more restrictive than those of younger patients undergoing CMT. Additionally, VAD may

represent the culmination of multiple insults to the artery, rather than the result of a single event.

Is the assertion of cause and effect consistent with our knowledge of the mechanisms of disease? The available evidence demonstrates that VAD as a result of CMT makes sense according to the biologic knowledge of the time. The biologic plausibility criterion is satisfactorily met and represents strong evidence for a cause-and-effect relationship between CMT and VAD.

Specificity: Is There One Cause for One Effect?

VAD cases in the literature commonly do not identify precipitating factors or causes and are alternatively classified spontaneous. Various VAD cases are described as being precipitated by common daily activities such as turning the head while driving, sneezing, playing tennis, kneeling to pray, and performing household chores. Other VAD cases are described as being associated with more vigorous activities such as yoga, archery, wrestling, swimming, sexual intercourse, trampoline jumping and other head and neck traumas.^{18,19} Additionally, concurrent pathologic conditions can frequently coexist with VAD, and may serve as predisposing risk factors. These risk factors can include hypertension, smoking, oral contraception, migraine, fibromuscular dysplasia, (FMD) Ehlers-Danlos syndrome, Marfan syndrome, cystic medial necrosis, disorders of collagen, α -1 antitrypsin deficiency, polycystic kidney disease, infection, vertebral artery redundancies, kinks, coils, or loops.⁷

Is there one cause for one effect in the association of VAD and CMT? We have concluded that there is not a single cause for VAD. Therefore, the specificity criterion is not confirmed. The absence of a positive finding for this criterion represents weak evidence against a causal association between CMT and VAD.

Is There an Analogous Cause-and-Effect Relationship Already Established for a Similar Exposure or Disease?

The analogy criterion calls for pre-existing evidence of a similar causal relationship. In the case of VAD, the most closely related form of disease is internal carotid artery dissection (ICAD). Several case series and case reports examine the causal relationship of ICAD and CMT.

The retrospective case series by Dzewas et al studied the outcome of patients with cervical artery dissection ($n = 126$). Of these patients, seventy 8 (62%) were found to have ICAD and 2 (1.6%) had simultaneous ICAD and VAD. Five (6%) of the 78 patients with ICAD had received CMT prior to the dissection and 1 (1.3%) of the patients with simultaneous ICAD and VAD received CMT prior to dissection. CMT had been performed prior to dissection more often in patients with VAD than in patients with ICAD. Furthermore, FMD was present in 18% of patients with ICAD, thus predisposing the patients to dissection even in the absence of CMT; although it is unclear if CMT aggravated the carotid artery to cause dissection or if dissection had occurred prior to administration of CMT.¹ Due to the unclear association of confounders and temporality, this study does not provide

sufficient support for a cause-and-effect relationship between ICAD and CMT.

The case series by Hufnagel et al¹³ presents 10 patients with stroke following CMT, of whom 2 patients (mean age 40 ± 5.5) presented with ICAD and 8 patients presented with VAD. One patient with ICAD sought CMT for complaint of headache and experienced stroke onset immediately after his first treatment. CMT was indicated by neck pain in the second patient with ICAD, who experienced stroke onset 16 hours after receiving his first treatment of CMT. Vascular risk factors include smoking and hyperlipidemia in the former, and no risk factors were present in the latter patient.¹³ Although this study demonstrates an association between ICAD and CMT, it exhibits selection bias because the investigators examined subjects who were known to have had stroke and CMT in close temporal proximity. Therefore, the evidence presented is weak in comparison to other retrospective case series.

Haldeman et al¹² presented a series of 64 cases that were referred to one of the authors for medico-legal review over a 16-year period. Two (3.3%) of the patients were found to have ICAD following CMT.¹² The authors do not disclose the details of the ICAD experienced by these 2 patients, rather they comment that ICAD associated with CMT is rare and that this occurrence is infrequently reported in the literature. Consequently, this case series presents weak evidence of a causal relationship for CMT and associated ICAD.

A review of the literature performed by Haneline et al⁷ concludes that there is not sufficient evidence to establish a causal relationship between ICAD and CMT. The authors speculate that numerous case reports, which are described as “class III” evidence, show that a temporal relationship does exist; however, the actual cause of ICAD is ambiguous due to confounding (eg, primary arteriopathy).⁷

Is there a well established analogous cause-and-effect relationship for a similar exposure? The answer is equivocal. While pieces of the literature support a moderately acceptable temporal association between ICAD and CMT, the relationship between CMT and ICAD is unclear due to a lack of strong evidentiary support. The analogy criterion is not satisfactorily met and its absence represents weak evidence against a cause-and-effect relationship between CMT and VAD.

EVIDENCE, RESULTS AND CRITICAL APPRAISAL: INCIDENCE OF CMT ASSOCIATED WITH VAD AND ISCHEMIC STROKE

To adequately answer the question of incidence, a prospective cohort study is needed in which a population that is free of VAD and stroke and has never been exposed to CMT is followed through a course of CMT and examined periodically to determine occurrences of VAD and stroke. To determine the incidence from this study, new cases of VAD and associated stroke after new exposure to CMT during the specified time period should be the numerator. The denominator should be comprised of all people of the cohort who are undergoing CMT and are present at the beginning of the observation period. A prospective cohort study such as this

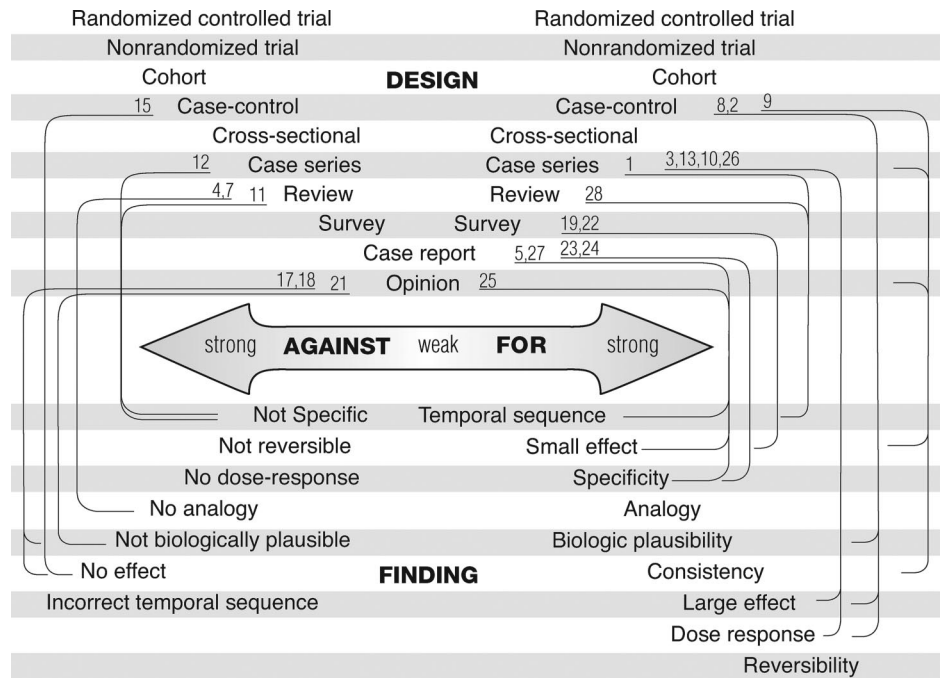


FIGURE 3. Depiction of how various studies on the topic of CMT and VAD are classified by research design as well as applicable findings.

does not exist. Published estimates of the incidence of VAD and stroke after CMT range from 1 in 5.8 million to 1 in 5000^{18,20} The best available estimate is from the case-control study by Rothwell et al,² which concludes that for every 100,000 persons <45 years of age who receive CMT, approximately 1.3 cases of vertebral artery dissection or occlusion attributable to CMT would be observed within 1 week of manipulative therapy.²

DISCUSSION

Weighing the Evidence

Most of this critically appraised topic was devoted to an examination of individual criterion for establishing a causal relationship. However, one must consider all the available evidence from all studies when drawing conclusions about cause. If the available study designs are weak to moderate and the evidence from different studies is conflicting at times, the decision requires judgment. In such cases, clinicians must decide where the weight of the evidence lies. Figure 3 summarizes the different types of evidence that explore causation, which are distinguishable by the research design and features that strengthen or weaken the evidence for cause. The figure depicts how various studies on the topic of CMT and VAD are classified by research design as well as applicable findings. Although there is evidence both for and against causality, the majority of the evidence supports a causal effect. Five of the applicable 7 criteria for causation are satisfied and support weak to moderate strength of evidence for causation between CMT and VAD and associated ischemic stroke, especially in young adults. Despite our rendering this judgment and conclusion, we continue to share the sentiment of our colleagues who plea for further research into both the benefits and the harms associated with CMT.²¹

This research, which would employ superior study designs, will be successful only if it is performed with a close collaboration between medical doctors, chiropractors and other CMT practitioners.²¹ In this study, medical doctors will need to clarify the role of other possible risk factors and confounders for VAD and stroke. Chiropractors will need to thoroughly define the specific CMT techniques used. Clinicians from all involved professions will need to approach this research trial with an unbiased position to accurately assess the favorable and unfavorable outcomes of CMT.

Clinical Bottom Lines

1. Five of the applicable 7 criteria for causation are satisfied and support weak to moderate strength of evidence for causation between CMT and VAD with associated stroke, especially in young adults. The criteria are listed in order of stronger to weaker: dose response, large effect, consistency, biologic plausibility, and temporal sequence.
2. From the largest of the 3 available case-control studies, young (<45 years) vertebrobasilar artery territory stroke patients were 5 times more likely than controls to have visited a chiropractor within 1 week of the event date (OR 5.03, 95% CI 1.32 to 43.87). No significant associations were found for those aged ≥45 years.
3. The best available estimate of the incidence, which is from a case-control study, states that for every 100,000 persons <45 years of age who receive CMT, approximately 1.3 cases of vertebral artery dissection or occlusion attributable to CMT would be observed within 1 week of manipulative therapy.
4. Ultimately, the acceptable level of risk associated with a therapeutic intervention like CMT must be balanced against evidence of therapeutic efficacy. Further research

that employs prospective cohort study designs is indicated to uncover both the benefits and the harms associated with CMT.

CONCLUSION

The evidence that both supports and negates a causal association between VAD and CMT has been thoroughly reviewed and appraised. The evaluated evidence includes case-control studies, prospective and retrospective case series, case reports, surveys, and expert commentaries, which comprises a weak to moderately strong platform from which to draw our conclusions. In summary, we have found the burden of evidence to support a cause-and-effect relationship between CMT with VAD and subsequent stroke. Although we confidently make this assertion based on the evidence presented, we agree that a comprehensive prospective study must be conducted in a collective effort between all CMT practitioners to further examine this causal relationship, the incidence of VAD and stroke caused by CMT and the therapeutic efficacy of CMT.

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APPENDIX

Mayo Clinic Evidence Based Clinical Practice, Research, Informatics, and Training (MERIT) Center Cofounders and Codirectors: Bart M. Demaerschalk and Dean M. Wingerchuk.

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Evidence Appraisers: Madeline L. Miley, Dean M. Wingerchuk, and Bart M. Demaerschalk.

Content Expert: Bart M. Demaerschalk.

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