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REVIEW

Effect of transcutaneous electrical nerve stimulation on hemodynamic variables: systematic review and meta-analysis

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Abstract:

Background: Transcutaneous electrical nerve stimulation (TENS) uses different combinations of frequency (low or high), excitation threshold (motor or sensory), and site of application (local or ganglion). **Objectives:** The present study aimed to investigate the acute effect of TENS on hemodynamic variables in different populations and to determine whether differences exist between low-frequency (< 10 Hz) and high-frequency (≥ 10 Hz) TENS, between motor and sensory excitability thresholds, and between local or ganglionic application. **Methods:** The Cochrane, EMBASE, SCOPUS, CINAHL, and PUBMED databases were searched for randomized clinical trials in which TENS was administered noninvasively with surface electrodes in the adult population (subjects aged 18 years or older). **Results:** Thirteen articles met eligibility criteria and included a total of 371 subjects. The outcomes were the effects of TENS on blood flow, peripheral vascular resistance, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP). A moderate increase in blood flow was noted when high frequencies were applied at the sensory threshold and above the ganglion. A decrease in peripheral vascular resistance was noted when TENS was administered at the sensory threshold above the ganglion. Significant changes in MBP and DBP were noted when high frequencies were administered at the sensory threshold and a significant difference in MBP was noted when TENS was administered locally. **Conclusion:** The results show that TENS can modify hemodynamic responses. Moreover, it is important to determine the frequency, excitability threshold, and site of application to achieve the expected results.

Keywords: Transcutaneous electrical nerve stimulation; blood flow; vascular resistance.

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BACKGROUND

Transcutaneous electrical nerve stimulation (TENS) is a noninvasive method that produces analgesic effects[1] and involves the administration of different combinations of frequency (low or high)[2], motor excitability threshold[3-8] or sensory excitability threshold[9-15] and local application site[3-17]. This method has been used in a variety of clinical contexts for the treatment of various acute and chronic conditions and is considered a recognized analgesic modality[1, 18]. Physiologically, some studies have shown that TENS may affect blood flow and mechanisms of vasodilation[15, 19] as well as blood pressure and heart rate[4, 7, 11, 15]. In addition, researchers indicate that the application of TENS over the stellate ganglion in the neck region between C7 and T4 can induce significant peripheral vasodilation[10, 14, 15, 19].

Recently, Mortensen et al. showed that TENS, applied over the stellate ganglion 30 minutes before exercise, attenuated the skeletal muscle metaboreflex by redistributing blood flow to the upper limbs 20 and increasing peripheral vasodilator capacity, resulting in a reduction in blood pressure at the end of exercise in healthy adolescents and older

adults[10, 15]. These effects were also demonstrated in patients after myocardial revascularization. They resulted in a significant improvement in functional capacity and showed greater efficacy in improving blood flow under conditions of low peripheral blood flow[10]. Therefore, TENS is thought to have a beneficial effect on the sympathetic nervous system and influence the pressure reflex[21]. Neuromodulation may vary depending on the duration, intensity, and location of application[12].

However, the literature is inconsistent on the use of these parameters. Researchers have not used them in a standardized manner, which increases the heterogeneity of the studies and makes it difficult to generalize the results. Studies have shown that changes in local circulation, such as myocardial oxygen supply and demand, depend on electrostimulation time[16, 19, 22]. Interestingly, authors have also noted other nonanalgesic effects, such as increased endogenous synthesis of vasodilators such as opioids[4, 23], sympathetic modulation[24, 25], and a reduction in peripheral vascular resistance[8]. Although these are isolated effects, these findings suggest that TENS may have an important influence on the increase in blood flow by altering the pressure reflex. These results support the hypothesis that TENS may be beneficial in various cardiovascular diseases such as arterial hypertension, myocardial ischemia, and heart failure.

Despite its cardiovascular effects, the use of TENS as a vasodilator has not been well established, mainly because few studies have compared the hemodynamic effects of TENS with a sham or control group. Accordingly, we believe that a meta-analysis comparing the vasodilatory effects of TENS with a sham or control group would be feasible and would help to determine clinical applicability more consistently. Therefore, the present study aimed to conduct a systematic review of studies addressing the effects of TENS on hemodynamic variables in different populations and to determine, whether differences exist between low-frequency (< 10 Hz) and high-frequency (≥ 10 Hz) TENS, between motor and sensory excitability thresholds, and between local or ganglionic application.

METHODS

Search strategy

We conducted a systematic review and meta-analysis in compliance with the recommendations and criteria described in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Cochrane Handbook[26]. The protocol was registered in the PROSPERO database (www.crd.york.ac.uk/prospero/) under number: CRD42014015484.

Sources of data

Potential studies were identified using a comprehensive strategy. Systematic searches were conducted in the following databases: The electronic databases Cochrane Library (online version 2015), PUBMED (1962-2021), CINAHL (1980-2021), SCOPUS (1980-2021), and EMBASE (1980-2021) were searched to identify eligible articles. The search was limited to randomized clinical trials, and a filter was used to limit the search to human trials. The sensitive search strategy was used to identify randomized clinical trials. Additional studies were identified by manually searching the reference lists of retrieved studies, review articles and textbooks. The following keywords were used for the systematic search: ("Transcutaneous Electric Nerve Stimulation"[Mesh] OR "Electric Stimulation Therapy"[Mesh] OR "electroacupuncture"[MeSH Terms]) NOT ("Cardiac Resynchronization Therapy"[Mesh] OR "Spinal Cord Stimulation"[Mesh] OR "Cardiac Pacing, Artificial"[Mesh] OR "Deep Brain Stimulation"[Mesh] OR "Electric Countershock"[Mesh] OR "Pulsed Radiofrequency Treatment"[Mesh] OR "Vagus Nerve Stimulation "[Mesh]) AND ("Blood Pressure"[Mesh] OR "hemodynamics"[MeSH Terms] OR

"vasodilation"[MeSH Terms] OR "Arterial Pressure"[Mesh] OR "Cardiovascular Physiological Phenomena"[Mesh]) AND ((Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial[ptyp] OR Pragmatic Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Research Support, American Recovery and Reinvestment Act[ptyp] OR Research Support, N I H, Extramural[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Research Support, Non U S Gov't[ptyp] OR Research Support, U S Gov't, Non P H S[ptyp] OR Research Support, U S Gov't, P H S[ptyp] OR Research Support, U.S. Government[ptyp]) AND "humans"[MeSH Terms] AND ("adult"[MeSH Terms] OR "young adult"[MeSH Terms] OR "adult"[MeSH Terms:noexp] OR ("middle aged"[MeSH Terms] OR "aged"[MeSH Terms]) OR "middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms])).

Selection of studies

Three reviewers analyzed the results independently. Articles found during the searches were first screened by title and abstract to exclude irrelevant studies. For prescreening, the abstract had to include the study design to facilitate identification, the appropriate population, and the relevant components of the intervention, as described above. The full texts of all potentially relevant randomized clinical trials were obtained and independently reviewed by the reviewers for eligibility based on the defined inclusion criteria. Studies that addressed outcomes during a specific stimulus (eg, the handgrip test) were included only if the effect of TENS was assessed before the stimulus[27]. The degree of disagreement was measured by the kappa statistic.

Types of studies and participants

Articles published in full-text journals with a randomized and/or controlled clinical design examining the effect of TENS on peripheral blood flow, peripheral vascular resistance, heart rate, and blood pressure (systolic, diastolic, and mean) were included in the present review. Clinical trials that examined a cohort of adults (18 years of age or older) who were considered healthy or who had been diagnosed with cardiovascular or metabolic disease were included for review. Studies that examined patients with a cancer diagnosis or spinal cord injury, interventions that used functional electrical stimulation, electroacupuncture, or noninvasive spinal cord stimulation, and studies that did not address the primary outcome were excluded from the review.

Types of intervention

Studies that involved a direct comparison of TENS with sham stimulation or a control modality were included in the review. Studies that examined TENS separately by stimulation frequency (low: less than 10 Hz; high: ≥ 10 Hz). TENS is an electrical current with a frequency between 1 and 250 hertz (Hz) applied noninvasively with surface electrodes. The sham intervention was defined as a treatment group using the same TENS equipment but without current. The control intervention was either the absence of treatment or a treatment modality other than TENS.

Outcome measures

The results used in this review were based on the main objective. We selected blood flow in absolute terms (ml/min) and excluded studies that assessed outcomes in relative terms (% or delta) or blood perfusion units. Vascular resistance was assessed in arbitrary units. Heart rate was evaluated as beats per minute (bpm) and blood pressure as mm Hg. All results were combined according to stimulation frequency, excitability threshold, and site of application.

Quality (risk of bias) and publication bias assessment

The risk of bias in eligible randomized clinical trials was assessed by a single reviewer and, in cases of doubt, reviewed by a second reviewer. Studies were independently classified by two reviewers (NM and LI) using the PEDro scale proposed by Verhagen et al.[28]. The PEDro scale analyzes eligibility criteria (not used to calculate the score), random allocation, concealed allocation, similarity at baseline, blinding of subjects, therapists, and reviewers, adequacy of follow-up, intention-to-treat analysis, statistical comparisons between groups, analyzes and reports of point estimates, and measures of variability.

Data extraction

Relevant data were extracted on inclusion criteria (study design, participants, type, duration, frequency, and intensity of electrical stimulation, pulse, site of application, comparisons, and outcomes), risk of bias (randomization, blinding, attrition, and control), and outcomes. For studies that compared the effect of two or more electrical variables (eg, two pulse rates, studies that determined the effect in cohorts with different characteristics, such as age, and studies that determined the effect more than once), only those that had the largest effect size were included. Data extraction was performed by a single reviewer and reviewed by a second reviewer. Disagreements were resolved by consensus. If necessary, the authors were contacted for further details on the results.

Statistical analysis

Data were processed based on the Cochrane Handbook for Systematic Reviews of Interventions[29]. For continuous variables, changes were compared using the weighted mean difference and 95% confidence interval (TENS group vs control group). The standard deviation was calculated for each study based on the change score method. Heterogeneity between studies was examined qualitatively by comparing the characteristics of the studies and quantitatively by using the chi-square heterogeneity test and the I2 statistic. Where appropriate, the results of the studies for each outcome were combined to determine the global estimate of the treatment effect. The effect model for the meta-analysis was selected based on the quantitative, qualitative, and publication bias analyses. All analyses were performed using Review Manager version 5.3.

RESULTS

Selection and evaluation of studies

The first search found 312 studies, of which 40 were duplicates. Two hundred ten studies were classified as potentially relevant based on the title and abstract. Seventy-five studies were subjected to full-text analysis, of which 62 were excluded[16, 17, 19, 22, 30-84]. Therefore, only 13 articles met the eligibility criteria[3-15]. Figure 1 shows the flowchart of the study selection process. The excluded studies and the reasons for exclusion are listed in Table 1.

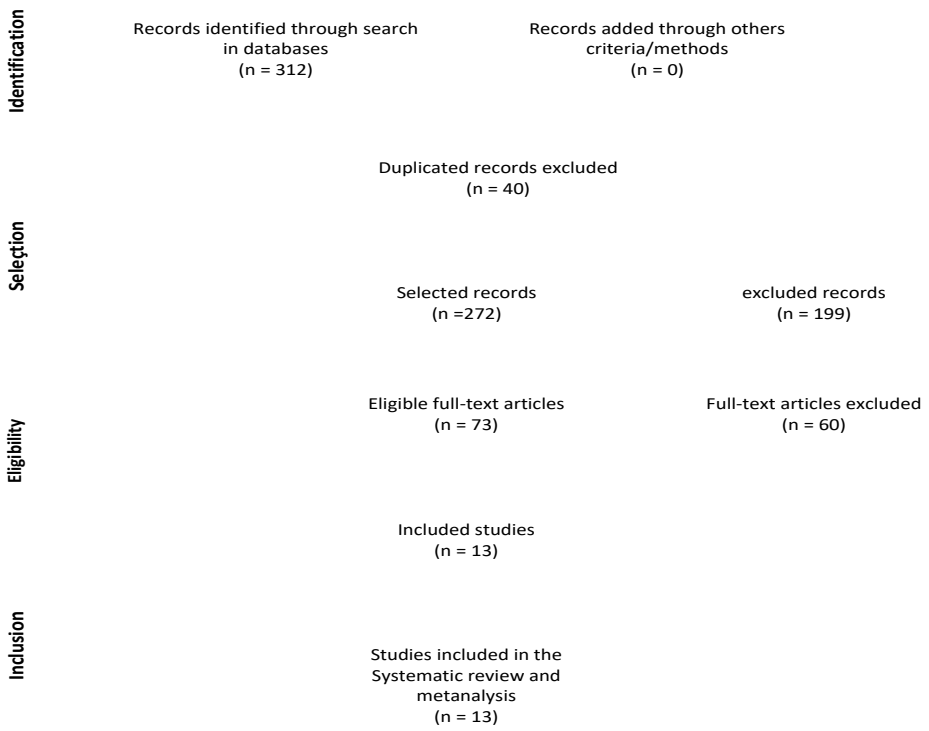

Figure 1. Flow chart of studies.

Table 1. Studies excluded and reasons for exclusion.

Studies	Reason for exclusion
Chauhan et al. 1994; Cheung et al. 2007; Jacobs et al. 1990; Jacobsson et al. 2000; Jessurun et al. 2003; Silverdal et al. 2012; Stein et al. 2011; Wikström et al. 1999.	No control group
Cramp et al. 2000; Cramp et al. 2002; Indergand et al. 1994; Kaada et al. 1990; Sandberg et al. 2007; Scudds et al. 1995; Tomasi et al. 2015.	Absence of absolute values
Bieuzen et al. 2012; Chi-Chen et al. 2009; Chih-Feng et al. 2003; Clancy et al. 2014; Czyrny et al. 2010; Dobšák et al. 2012; Eschweiler et al. 2000; Farese et al. 2008; Gazelius et al. 2002; Hideaki et al. 2015; Hsiao et al., 2008; Indergand et al. 1995; Jung et al. 2011; Kemler et al. 2000; Khalil et al. 2007; Lawson et al. 2007; Meglic et al. 2011; Ming Ho et al. 2009; Ngai et al. 2013; Noble et al. 2000; Perlmutter et al. 2002; Speer et al. 2000; Spincemille et al. 2000; Thijssen et al. 2007; Tordoir et al. 2007; Townsend et al. 2011; Yu-Xia et al. 2010; Zheng et al. 2014; Zheng-qin et al. 2014.	Did not use TENS as main current.
Chen et al. 2007; Forst et al. 1997; Izumi et al. 2010; Johnson et al. 1991; Laan et al. 2010[20]; McDowell et al. 1999; Ngai et al. 2010.	Mean and standard deviation values not expressed
Franco et al. 2014; Hallén et al. 2010; Maggie et al. 2011; Sanderson et al. 1995.	Did not present values before and after administration of TENS.
Vilela-Martin et al. 2016	Protocol study
Kamali et al. 2017	Flow not evaluated as mL/min
Kjartansson et al. 1990	Not a clinical trial
Bertalhanfy et al. 2005; Jones et al. 2014.	Used TENS during exercise

Studies included in systematic review

Table 2 shows the average characteristics of all studies. The publication dates of the included studies ranged from 1984 to 2019 and included a total of 371 subjects, of whom 273 (68.7%) were male. The mean age was 29.2 ± 4.5 years and 32.6 ± 5.0 years for the healthy intervention and control groups, respectively. For groups that included patients with cardiovascular disease, the mean age was 56.5 ± 10.3 years and 61.9 ± 8.5 years for the intervention and control groups, respectively. Nine studies[3, 4, 6-9, 12, 14] recruited healthy subjects, and four studies examined patients with cardiovascular disease [5, 10, 11, 13]. Analysis of quality using the PEDro scale yielded scores ranging from 4 to 10. Overall, the quality of the majority of studies was rated as good (Table 3). The degree of interviewer agreement, calculated using the kappa coefficient, was 0.91 (95% CI 0.79-1.0).

Intervention

High-frequency (≥ 10 Hz) TENS was used more frequently. Five studies compared the effects of HF TENS with a control group[3, 7-9, 13]. Four studies compared the effects of HF with LF TENS[3, 4, 8, 11]. Two studies compared the effects of LF TENS with a control group[3, 8]. Seven studies compared the effects of HF TENS with sham stimulation[4, 5, 10-12, 14, 15] and three studies compared the effects of LF TENS with sham stimulation[4, 6, 11]. The results were heterogeneous concerning the site of application of the electrodes: in the cervicothoracic sympathetic ganglion area in four studies[10, 11, 14, 15], at acupuncture points in five studies[4, 7-9, 13] and the lower limbs in three studies[3, 6, 12]. Table 3 provides an overview of the interventions used in the different studies.

Effect of TENS

The analyses of hemodynamic responses were performed according to the following TENS parameters: a) low and high frequency; b) motor or sensory excitability threshold; and c) local or ganglionic site of application.

Hemodynamic responses according to TENS frequency

Blood flow

For blood flow analysis, we found only one study that used low-frequency TENS[8] and four studies that used high-frequency TENS[7, 8, 10, 15]; one study compared young and older adults[14, 15]. Overall, both LF and HF were associated with significant increases in blood flow (four studies, n = 176 subjects, weighted mean difference [WMD] = 0.52 ml/min, 95% confidence interval [CI] of 0.11 to 0.92 ml/min, I^2 = 79%) (Figure 2a). However, in the isolated analysis, the results of the analysis for LF were inconclusive (01 study, n = 40 subjects, WMD = 0.00 ml/min and 95% CI: -0.79 to 0.79 ml/min; I^2 = not applicable), whereas in the high-frequency analysis, an increase in blood flow was observed (Four studies, n = 136 subjects, WMD = 0.71 ml/min, 95% CI: 0.23 to 1.18 ml/min, I2 = 81%).

Peripheral vascular resistance and heart rate

In the analysis of vascular resistance, neither LF nor HF was associated with improved PVR (Total: three studies, n = 98 subjects, WMD = -10.11 arbitrary units, 95% CI: -22.79 to 2.57 arbitrary units, I^2 = 83%; LF: 01 study, n = 40 subjects, WMD = -1.20 arbitrary units, 95% CI: -17.14 to 14.74 arbitrary units, I^2 = not applicable; HF: 02 studies, n = 58 subjects, WMD = -12.85 arbitrary units, 95% CI: -29.45 to 3.75 arbitrary units, I^2 = 88%) (Figure 2b). Similarly, HF and LF were not associated with HR in all analyses (total: n = 262 subjects, WMD = 0.00 bpm, 95% CI: -2.00 to 1.99 bpm, I^2 = 0%; LF: n = 40 subjects, WMD = -0.16 bpm, 95% CI: -8.75 to 8.44 bpm, I^2 = 0%; HF: n = 222 subjects, WMD = 0.01 bpm, 95% CI: -2.04 to 2.06 bpm, I^2 = 0%) (Figure 2c).

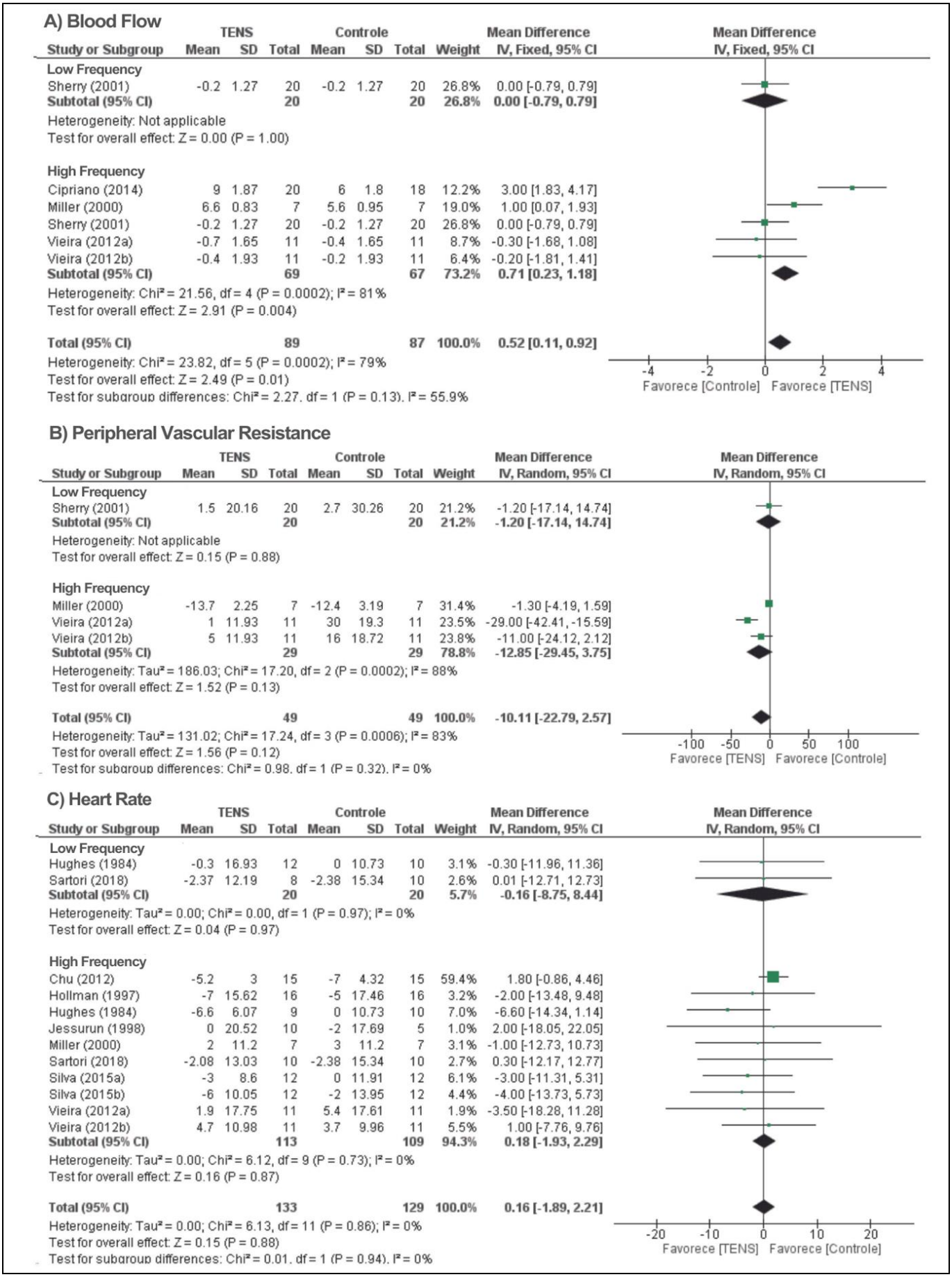

Figure 2. Forest plot comparing effects of low-frequency and high-frequency TENS on blood flow (A), peripheral vascular resistance (B), and heart rate (C). [Blood flow; Control; Low Frequency; High Frequency; Peripheral vascular resistance; Heart rate; Favors TENS; Favors Control].

Arterial pressure results

Mean blood pressure

The analysis of mean blood pressure (MBP) included only studies that used high-frequency TENS[5, 7, 10, 15], of which one compared young and older adults[15]. The analysis showed a significant reduction in MBP when high-frequency TENS was used (04 studies, n=142 subjects, WMD = -9.45 mmHg, 95% CI: -15.64 to -3.26 mmHg, I^2 = 38%) (Figure 3a).

Systolic blood pressure

Four studies investigated the effect of low-frequency TENS on systolic blood pressure (SBP)[3, 4, 6, 11] and eight studies investigated the effect of high-frequency TENS[3-5, 9, 11, 12, 14], two of which compared young and older adults[14, 15]. Overall analysis showed inconclusive results (12 studies, n = 499 subjects, WMD = -1.01 mmHg, 95% CI: -4.79 to 2.78 mmHg, I^2 = 98%). In subgroup analysis, LF TENS showed a reduction in SBP (n = 170 subjects, WMD = -3.39 mmHg, 95% CI: -4.98 to -1.79 mmHg, I^2 = 9%). However, the HF TENS was inconclusive (n = 329 subjects, WMD = -0.19 mmHg, 95% CI: -3.77 to 3.40 mmHg, I^2 = 67%) (Figure 3b).

Diastolic blood pressure

Three studies analyzed the effect of low-frequency TENS on diastolic blood pressure (DBP)[4, 6, 11] and seven studies analyzed the effect of high-frequency TENS[4, 5, 9, 11, 12, 14, 15], two of which compared young and older adults[14, 15]. TENS intake was associated with a decrease in DBP in both the overall and HF TENS analyses (overall: n = 319 subjects, WMD = -2.81 mmHg, 95% CI: -4.44 to -1.18 mmHg, I^2 = 0%; HF: n = 239 subjects, WMD = -2.85 mmHg, 95% CI: -4.66 to -1.03 mmHg, I^2 = 0%). However, the results of the low-frequency TENS were inconclusive (n = 80 subjects, WMD = -2.66 mmHg, 95% CI: -6.38 to 1.07 mmHg, I2 = 0%) (Figure 3c).

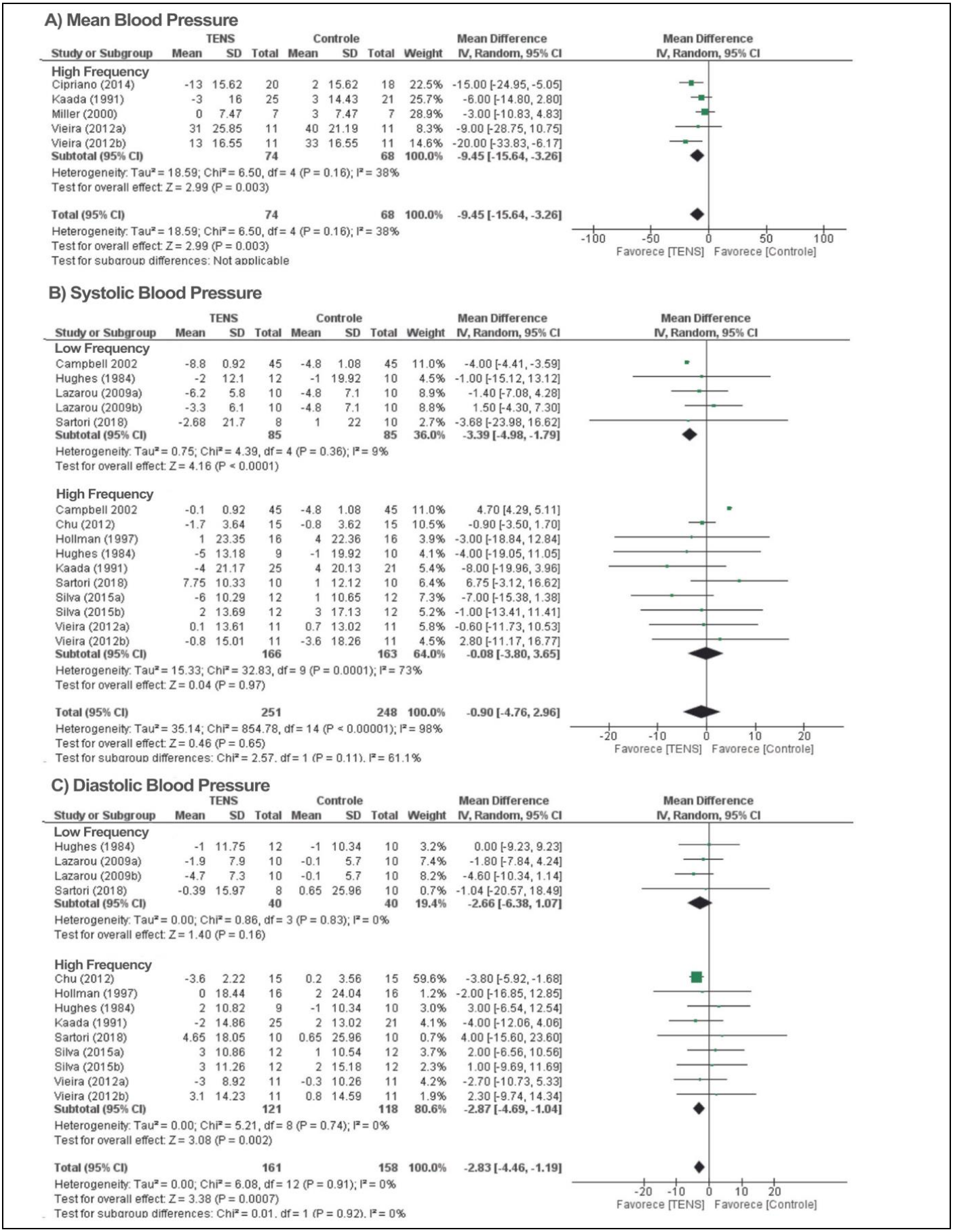

Figure 3. Forest plot comparing effects of low-frequency and high-frequency TENS on mean blood pressure (A), systolic blood pressure (B), and diastolic blood pressure (C). [Mean blood pressure; Control; Low Frequency; High Frequency; Systolic blood pressure; Diastolic blood pressure; Favors TENS; Favors Control].

Motor or sensory excitability threshold

Blood flow

Two studies analyzed blood flow using TENS at the motor excitability threshold[7, 8] and two studies used TENS at the sensory threshold[10, 15], one of which compared young and older adults[15]. In the overall analysis, a significant increase in blood flow was found (n = 136 individuals, WMD = 0.79 ml/min, 95% CI: 0.29 to 1.29 ml/min, I^2 = 80%). In the subgroup analysis, the effect of the motor excitability threshold was inconclusive (02 studies, n = 54 individuals, WMD = 0.42 ml/min, 95% CI: -0.19 to 1.02 ml/min, I^2 = 61%). In contrast, blood flow increased when the sensory threshold was used (n = 82 individuals, WMD = 1.61 ml/min, 95% CI: 0.72 to 2.50 ml/min, I^2 = 85%) (Figure 4a).

Peripheral vascular resistance and heart rate

Two studies analyzed peripheral vascular resistance using TENS at the motor excitability threshold[7, 8] and two studies used TENS at the sensory threshold[10, 15], one of which compared young and older adults[15]. In the overall analysis, there was a significant decrease in peripheral vascular resistance (04 studies, n = 136 individuals, WMD = -4.79 arbitrary units, 95% CI: -7.45 to -2.13 arbitrary units, I^2 = 93%). In the subgroup analyses, the effect of the motor threshold was inconclusive (02 studies, n = 54 individuals, WMD = -1.30 arbitrary units, 95% CI: -4.14 to 1.55 arbitrary units, I^2 = 0%) whereas the sensory threshold led to a significant reduction in peripheral vascular resistance (02 studies, n = 82 individuals, WMD = -28.50 arbitrary units, 95% CI: -35.91 to -21.09 arbitrary units, I^2 = 84%) (Figure 4b).

Two studies analyzed heart rate using TENS at the motor excitability threshold[4, 7], and seven studies used TENS at the sensory threshold 9,11-15, two of which compared young and older adults[14, 15]. The results of both overall and subgroup analysis were inconclusive (Overall: 09 studies, n = 262 individuals, WMD = -0.32 bpm, 95% CI: -2.34 to 1.70 bpm, I^2 = 0%; Motor: 02 studies, n= 55 individuals, WMD = -3.82 bpm, 95% CI: -9.47 to 1.83 bpm, I^2 = 0%; Sensory: 07 studies, n= 207 individuals, WMD = 0.19 bpm, 95% CI: -1.97 to 2.35 bpm, I^2 = 0%) (Figure 4c).

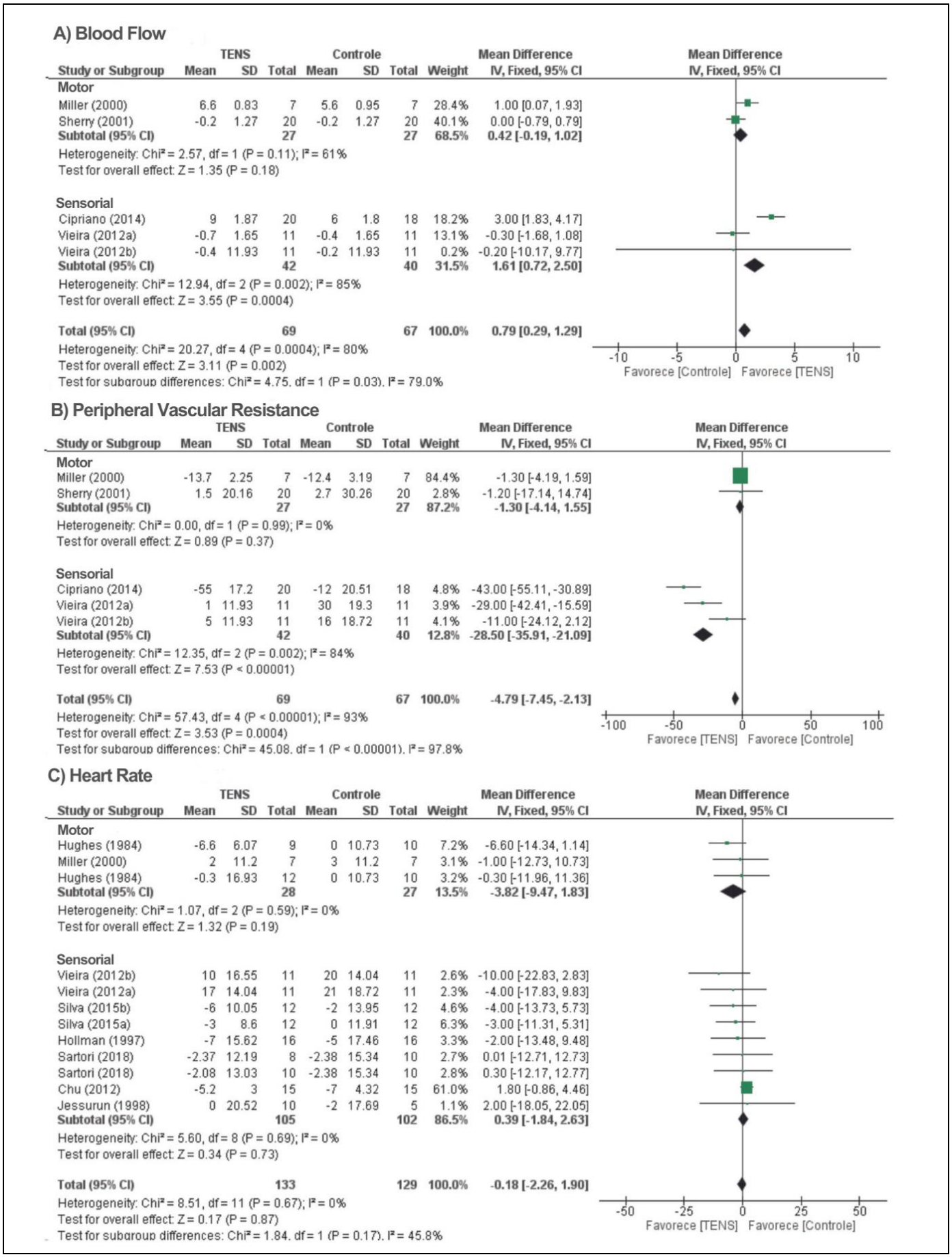

Figure 4. Forest plot comparing the effect of TENS at motor and sensory thresholds on blood flow (A), peripheral vascular resistance (B), and heart rate (C). [Blood flow; Control; Sensory; Low Frequency; High Frequency; Peripheral vascular resistance; Heart rate; Favors TENS; Favors Control].

Arterial pressure results

Mean blood pressure

Two studies analyzed mean blood pressure using TENS at the motor excitability threshold[5, 7] and two used TENS at the sensory level[10, 15], one of which compared young and older adults[15]. In the overall analysis, TENS led to a significant reduction in MBP (04 studies, n = 104 individuals, WMD = -6.86 mmHg, 95% CI: -12.06 to -1.66 mmHg, I^2 = 33%). In the subgroup analyses, the effect of TENS at the motor threshold was inconclusive (02 studies, n = 60 individuals, WMD = -4.32 mmHg, 95% CI: -10.17 to 1.52 mmHg, I^2 = 0%), whereas a significant reduction in MBP was found when TENS was used at the sensory threshold (02 studies, n = 44 individuals, WMD = -16.38 mmHg, 95% CI: -27.71 to -5.05 mmHg, I^2 = 0%) (Figure 5a).

Systolic blood pressure

Four studies analyzed systolic blood pressure using TENS at the motor excitability threshold [3-6], and six studies used TENS at the sensory level [9, 11, 12, 14], one of which compared young and older adults 15. In the overall analysis, a significant reduction in SBP was found (10 studies, n = 365 individuals, WMD = 0.31 mmHg, 95% CI: 0.02 to 0.60 mmHg, I^2 = 98%). In the subgroup analyses, TENS at the motor threshold led to a reduction in SBP (n = 217 individuals, WMD = -0.34 mmHg, 95% CI: 0.05 to 0.63 mmHg, I^2 = 99%), whereas the effect of the sensory threshold was inconclusive (n = 148 individuals, WMD = -1.45 mmHg, 95% CI: -3.80 to 0.91 mmHg, I^2 = 0%) (Figure 5b).

Diastolic blood pressure

Three studies analyzed diastolic blood pressure using TENS at the motor excitability threshold[4-6], and four studies used TENS at the sensory level[9, 11, 12, 14], one of which compared young and older adults 14. In the overall analysis, a significant reduction in DBP was found (n = 275 individuals, WMD = -2.93 mmHg, 95% CI: -4.62 to -1.24 mmHg, I^2 = 0%). In the subgroup analyses, a significant reduction in DBP occurred with TENS was used at the sensory threshold (n = 148 individuals, WMD = -3.18 mmHg, 95% CI: -5.17 to -1.20 mmHg, I^2 = 0%), whereas the effect of the motor threshold was inconclusive (n = 127 individuals, WMD = -2.27 mmHg, 95% CI: -5.50 to 0.96 mmHg, I^2 = 0%) (Figure 5c).

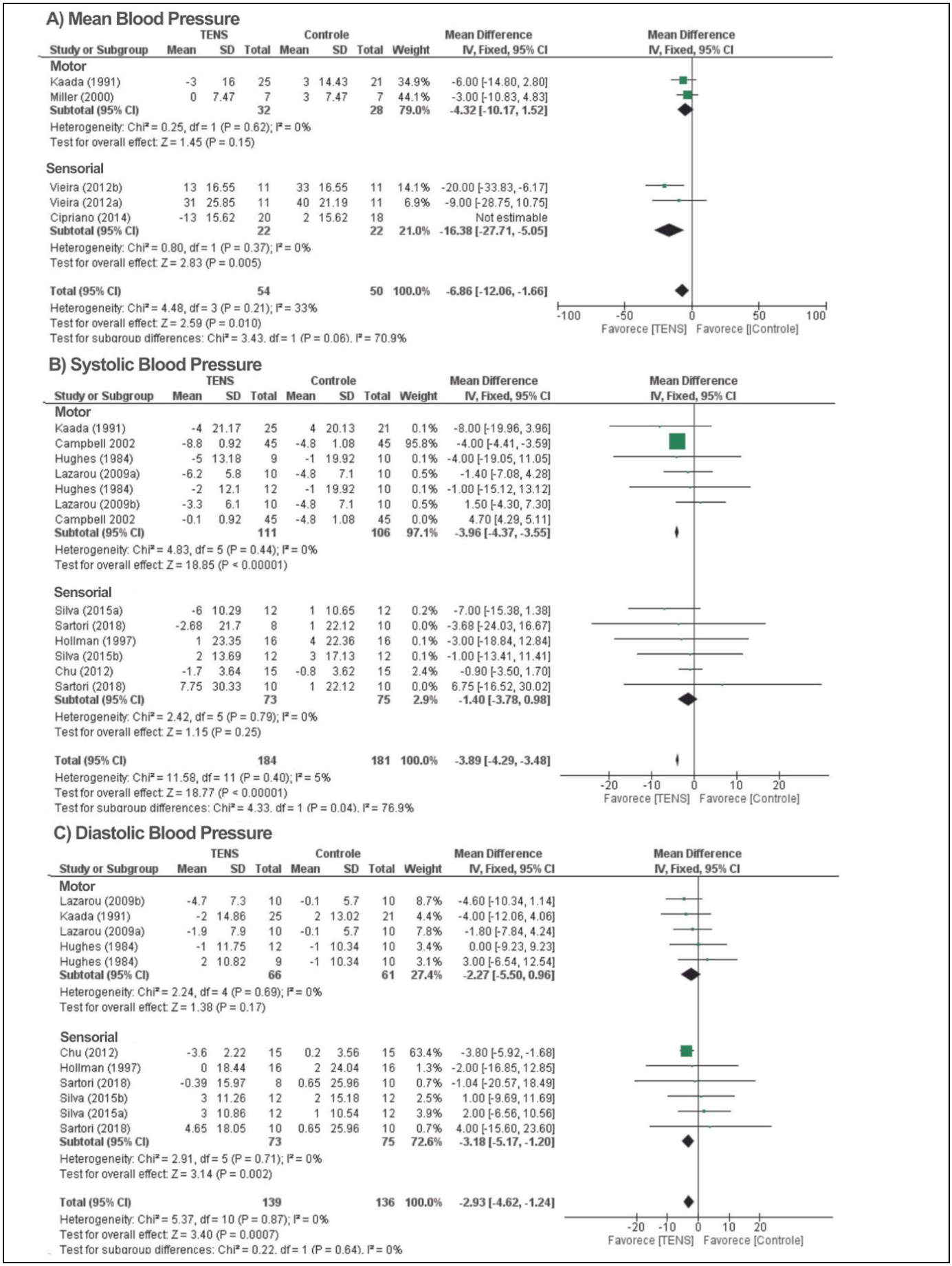

Figure 5. Forest plot comparing the effect of TENS at motor and sensory thresholds on mean blood pressure (A), systolic blood pressure (B), and diastolic blood pressure (C). [Mean blood pressure; Control; Sensory; Low Frequency; High Frequency; Systolic blood pressure; Diastolic blood pressure; Favors TENS; Favors Control].

Local or ganglion application site

Blood flow

Three studies analyzed blood flow using TENS applied locally[7, 8, 13] and two used TENS applied in the ganglion region[10, 15], one of which compared young and older adults 15. Despite of significant increase in blood flow in the subgroup analyses ganglion application (02 studies, n = 82 individuals, WMD = 1.61 ml/min, 95% CI: 0.73 to 2.50 ml/min, I^2 = 84%), results of the overall (05 studies, n = 151 individuals, WMD = 0.58 ml/min, 95% CI: 0.16 to 1.01 ml/min, I^2 = 78%) and local application (03 studies, n = 69 individuals, WMD = 0.27 ml/min, 95% CI: -0.21 to 0.76 ml/min, I^2 = 42 subgroup %) analysis were inconclusive (Figure 6a).

Peripheral vascular resistance and heart rate

Two studies analyzed peripheral vascular resistance using TENS applied locally[7, 8], and two used ganglion application 10,15, one of which compared young and older adults[15]. In the overall analysis, peripheral vascular resistance was significantly reduced (04 studies, n = 136 individuals, WMD = -5.10 arbitrary units, 95% CI: -7.47 to -2.74 arbitrary units, I^2 = 86%). In the subgroup analyses, the effect of locally applied TENS was inconclusive (02 studies, n = 54 individuals, WMD = -1.30 arbitrary units, 95% CI: -4.14 to 1.55 arbitrary units, I^2 = 0%), whereas ganglion application led to a significant reduction in peripheral vascular resistance (02 studies, n = 82 individuals, WMD = -13.60 arbitrary units, 95% CI: -17.86 to -9.35 arbitrary units, I^2 = 65%) (Figure 6b).

Five studies analyzed heart rate using TENS applied locally[4, 7, 12, 13], and for used ganglion application 11,14,15, two of which compared young and older adults[14, 15]. Both overall and subgroup analysis don't result in significant change in heart rate (Overall: 09 studies, n = 232 individuals, WMD = -3.27 bpm, 95% CI: -6.59 to 0.06 bpm, I^2 = 0%; Local application: 05 studies, n = 102 individuals, WMD = -3.14 bpm, 95% CI: -8.05 to 1.78 bpm, I^2 = 0%; Ganglion application: 04 studies, n = 130 individuals, WMD = -3.38 bpm, 95% CI: -7.90 to 1.14 bpm, I^2 = 0%) (Figure 6c).

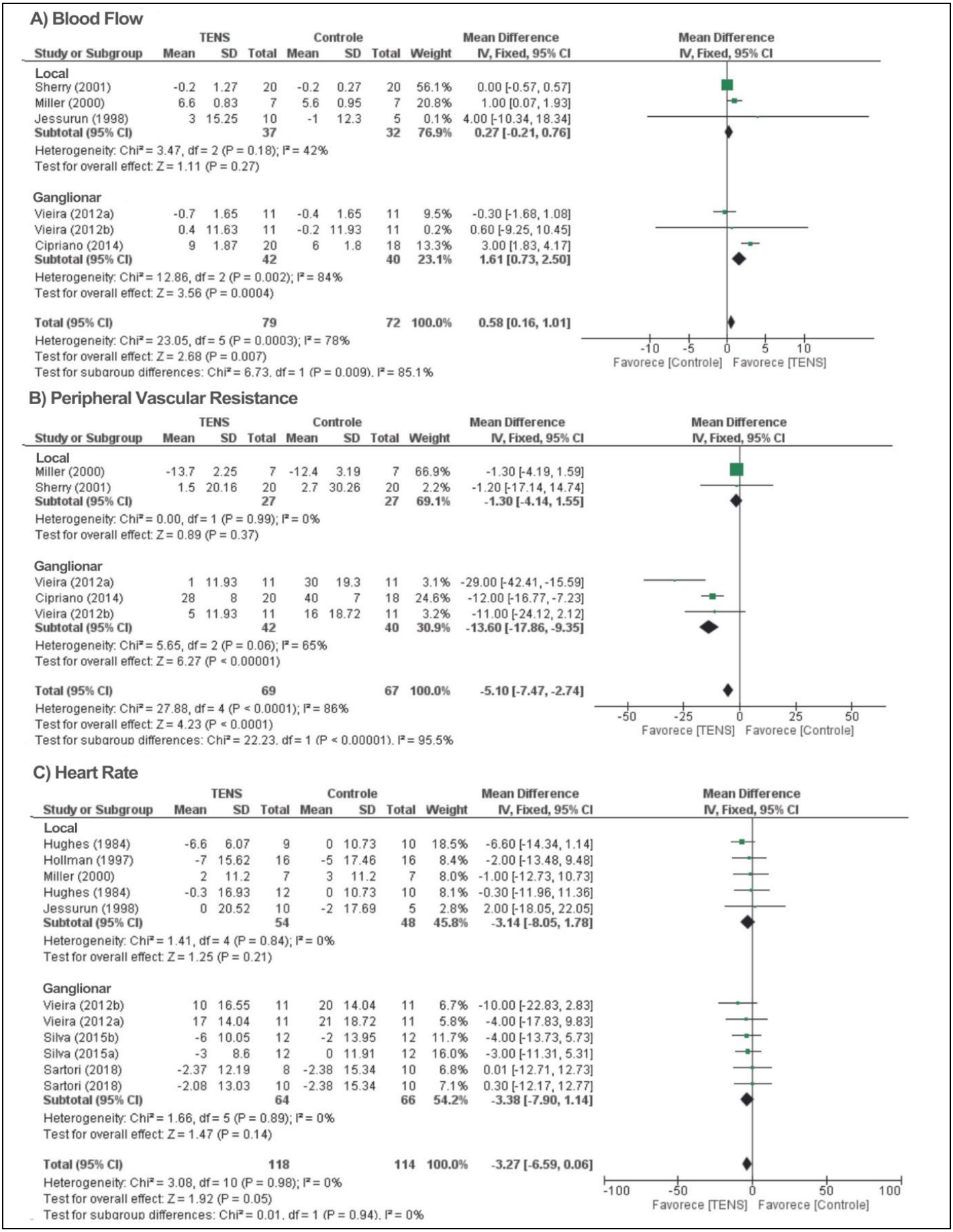

Figure 6. Forest plot comparing the effect of TENS applied locally or over ganglion on blood flow (A), peripheral vascular resistance (B), and heart rate (C). [Blood flow; Control; Ganglion; Low Frequency; High Frequency; Peripheral vascular resistance; Heart rate; Favors TENS; Favors Control].

Arterial pressure results

Mean blood pressure

Two studies analyzed mean blood pressure using TENS applied locally[5, 7] and two applied TENS over the stellate ganglion[10, 15], one of which compared young and older adults[15]. In the overall analysis, TENS led to a significant reduction in MBP (04 studies, n = 142 individuals, WMD = -8.61 mmHg, 95% CI: -13.21 to -4.00 mmHg, I^2 = 38%). In the subgroup analyses, only ganglion application led to a significant reduction in MBP (n = 82 individuals, WMD = -15.6 mmHg, 95% CI: -23.08 to -8.13 mmHg, I^2 = 0%) whereas the effect of locally applied TENS was inconclusive (n = 60 individuals, WMD = -4.32 mmHg, 95% CI: -10.17 to 1.52 mmHg, I^2 = 0%), whereas (Figure 7a).

Systolic blood pressure

Studies analyzed systolic blood pressure using TENS applied locally[4, 5, 12], and three used ganglion application[11, 14], one of which compared young and older adults[14]. In the overall analysis, a significant reduction in SBP was found (07 studies, n = 205 individuals, WMD = -4.50 mmHg, 95% CI: -9.31 to -0.31 mmHg, I^2 = 0%). However, in the subgroup analyses, the effects of local application (n = 119 individuals, WMD = -4.44 bpm, 95% CI: -11.44 to 2.56 bpm, I^2 = 0%) and ganglion application (n = 86 individuals, WMD = -4.55 bpm, 95% CI: -11.17 to 2.07 bpm, I^2 = 0%) were inconclusive (Figure 7b).

Diastolic blood pressure

Studies analyzed diastolic blood pressure using TENS applied locally (4, 5, 12), one of which analyzed low-frequency and high-frequency TENS (4), and three applied TENS over the stellate ganglion (11, 14), one of which compared young and older adults (14) and one analyzed low-frequency and high-frequency TENS (11). In the overall analysis, no significant change was found (n = 205 individuals, WMD = 0.09 mmHg, 95% CI: -3.69 to 3.86 mmHg, I^2 = 0%). Moreover, in the subgroup analyses, the effects of local application (n = 119 individuals, WMD = -0.88 bpm, 95% CI: -5.73 to 3.96 bpm, I^2 = 0%) and ganglion application (n = 86 individuals, WMD = 1.58 bpm, 95% CI: -4.44 to 7.60 bpm, I^2 = 0%) were inconclusive (Figure 7c).

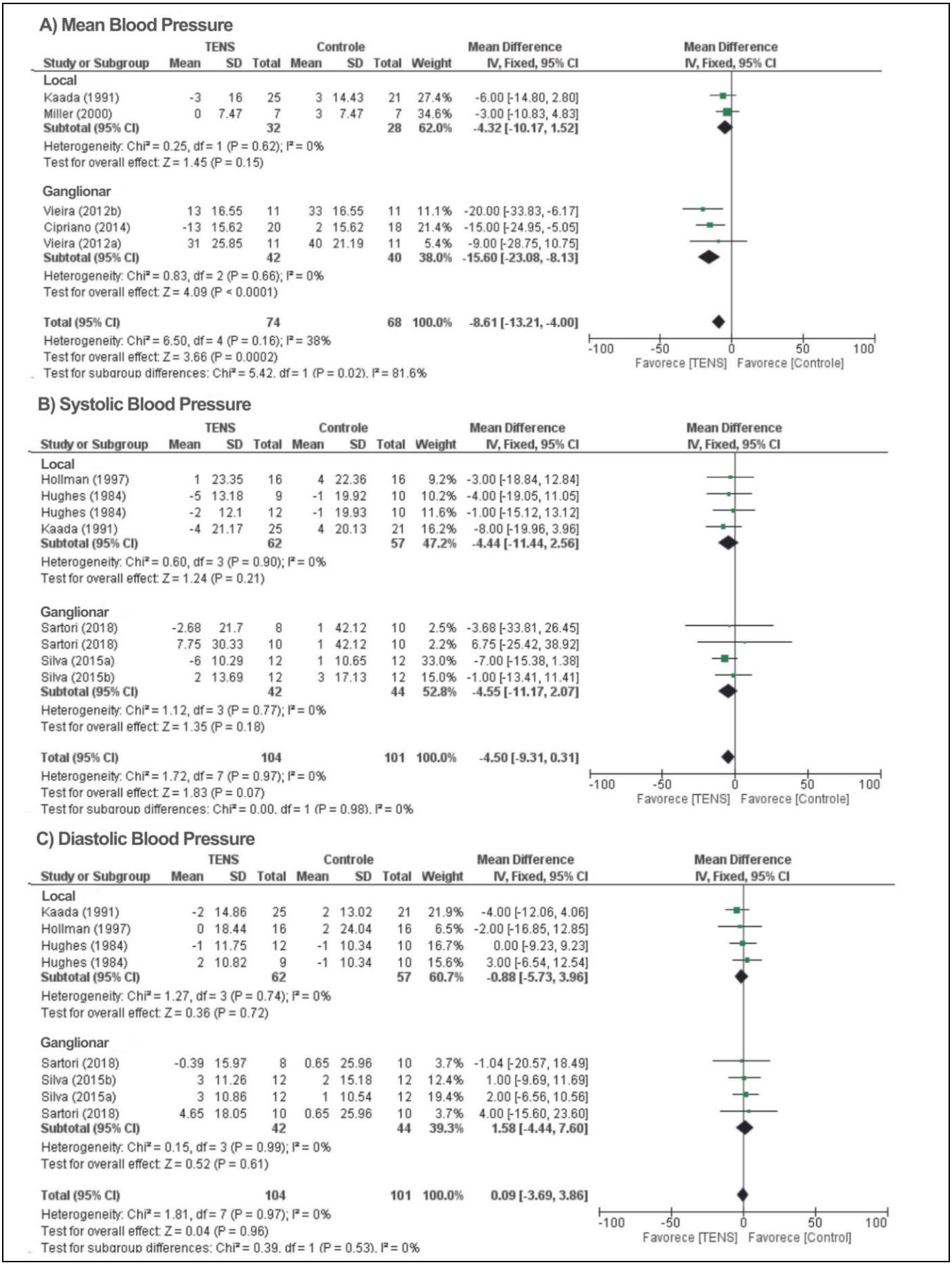

Figure 7. Forest plot comparing the effect of TENS applied locally or over ganglion on mean blood pressure (A), systolic blood pressure (B), and diastolic blood pressure (C). [Mean blood pressure; Control; Ganglion; Low Frequency; High Frequency; Systolic blood pressure; Diastolic blood pressure; Favors TENS; Favors Control].

DISCUSSION

The present review examined the effect of TENS on blood flow, peripheral vascular resistance, heart rate, and blood pressure responses in apparently healthy individuals and patients with cardiovascular disease in randomized double-blind clinical trials. TENS with HF and sensorial threshold had a satisfactory effect on blood flow and diastolic blood pressure. Moreover, changes in peripheral vascular resistance and mean blood pressure occurred with the application of ganglionic TENS and sensory threshold. Finally, the application of TENS did not affect the HR variable.

These findings may be linked to the hypothesis that TENS has a vasodilatation effect, increasing both local and peripheral blood flow when applied at HF, depending on the site where the current is applied. Moreover, TENS applied at the sensory threshold reduced peripheral vascular resistance, corroborated with Chen et al.[62] resulting in significant improvements in blood flow. In contrast, the application motor failed to show any effect on blood flow. This response may be associated with a greater capacity to produce analgesia with TENS-HF even in situations of high tolerance to the use of other opioids such as morphine when compared to the use of low-pacing frequencies[85].

Furthermore, it is known that the response of blood flow and vascular resistance improvement is directly dependent on blood pressure. TENS applied at HF significantly reduced both MBP and DBP (by around 9.45 and 2.87 mmHg, respectively), while LF reduced only SBP (3.39 mmHg) (Figure 2). The effects of blood pressure reduction reported in this meta-analysis are only slightly higher than those achieved with well-established interventions, such as aerobic exercise, which has been demonstrated to reduce systolic and diastolic blood pressure by 3.84 and 2.58 mmHg, respectively[86], being considered clinically significant[87, 88]. Another meta-analysis reports that, in normotensive subjects, the standard dose of an anti-hypertensive drug produces an estimated 5.7 mmHg reduction in systolic blood pressure and a 3.6 mmHg in diastolic blood pressure[89]. According to the authors, a 10 mmHg reduction in systolic pressure or 5 mmHg reduction in diastolic pressure using any of the main classes of blood pressure medication reduces cardiovascular disease by one-quarter and stroke by one-third, independently of the presence or absence of vascular disease or arterial hypertension before treatment[89].

Thus, patients with heart failure or coronary artery disease could benefit from this therapy due to the sympathetic inhibitory effect induced electrically by high-frequency TENS. Several researchers have hypothesized that TENS at different intensities and frequencies can reduce sympathetic activity and produce the local release of endothelial factors that provoke greater vascular relaxation[4, 24, 25, 71, 90]. The sympathetic inhibitory effect produced by high-frequency TENS is explained by a functional reduction in the sensitivity of nicotinic receptors located on the ganglion level of sympathetic fibers[24, 25, 71, 91, 92]. Another possible mechanism is the release of endogenous vasodilators, which is explained by the antidromic activation of sensory fibers by low-frequency TENS.

The depolarization of sensory nerve endings induced by antidromic electrical current seems to trigger the release of endothelial factors that act on the target organ of the stimulated fiber[91, 93, 94]. Both mechanisms may be involved in the hemodynamic effects induced by TENS and may be associated with other effects, such as pain relief and an increase in the recruitment of collateral blood vessels.

The magnitude of the hemodynamic effects induced by TENS may depend on both the frequency and application site. Different application sites target different organs, with different effects achieved on the peripheral[8, 15, 24, 25, 71], cardiac[95, 96] and systemic[97] levels. However, the small number of studies that have addressed the influence of TENS on blood pressure and heart rate and the significant differences in the methods employed in these studies diminish our ability to perform more robust analyses. Nonetheless, the present meta-analysis demonstrates the blood pressure-reducing effect of high-frequency TENS when applied at the sensory threshold and in the ganglion region.

In our study, it was evident that the application of TENS in the cervicothoracic region (ganglion) results in increasing blood flow. Cipriano Júnior et al.[10] tested the hypothesis that TENS applied over the stellate ganglion 24 hours after myocardial revascularization surgery has both analgesic capacity and contributes to the vascularization of the tissues by increasing blood flow. The authors found that TENS reduced sympathetic activity and increased blood flow by up to 50% in patients with peripheral vascular disease. Vieira et al.[15] performed the application of high-frequency TENS in the cervicothoracic (ganglion) region in healthy young and older adults with an effective increase in the blood flow redistribution associated with a reduction in sympathetic/parasympathetic balance[15]. Also, Jessurun et al.[13] studied the effect of high-frequency TENS on coronary vasomotricity in patients with angina. TENS was applied to the lower back region for approximately six minutes and all patients exhibited a 90% reduction in the lumen of the anterior descending coronary artery. The authors concluded that TENS can be used in patients with coronary stenosis to improve the metabolism and increase the velocity of coronary flow at rest, thereby promoting the oxygenation of the myocardium due to the coronary vasomotricity effect. These findings agree with the results of the present meta-analysis and confirm the hypothesis that TENS has important vasodilatation effects.

On the other hand, the application of TENS has not resulted in a minimal gain in blood flow or vascular resistance. However, when we individually analyze the studies, Sherry et al.[8] found that TENS administered at an intensity 25% above the motor threshold caused a "transitory" increase in blood flow, which did not occur when applied at or below the motor threshold. Indergand et al.[19] failed to show any benefit in increasing local blood flow with the application of 30 minutes of high-frequency and low-frequency TENS in the tibial and peroneal nerves (locally). Miller et al.[7] compared the effect of TENS and voluntary muscle contraction regarding the degree of activation and increase in blood flow, applying the electrodes over the tibial nerve in healthy adults aged 18 to 49 years for approximately ten minutes. The authors found an increase in blood flow and consequent reduction in peripheral vascular resistance measured in the calf during both voluntary contraction and TENS. However, it was observed with different durations, where the effects of TENS on the first day was 230% and on the second day 191%, whereas the voluntary contraction on the first day was 137% on the second day 149%, and fifteen minutes after exercise, TENS duration was 72% and 81% when compared to the voluntary contraction protocol, which presented 29% and 38%, but this study concludes that TENS is no more effective than voluntary exercise.

In the present meta-analysis, the hemodynamic effects induced by TENS were investigated in groups based on the type of electrical current and population analyzed. A high-frequency TENS proved to have a better effect on the increase in blood flow compared to low-frequency TENS. About blood pressure, low-frequency TENS had a better effect on modulating systolic blood pressure, whereas high-frequency TENS had a better effect on modulating diastolic blood pressure. These findings may be partially explained by the possible normal sympathetic tone in apparently healthy individuals, who may have a greater hemodynamic response to endogenous vasodilators released during low-frequency TENS than the sympathetic inhibition induced by high-frequency TENS, but this aspect requires further investigation.

Limitations of the study

The present study has limitations that should be considered. The scarcity of studies published on this topic, the poor quality of the studies selected, the lack of standardization in the methods, and the considerable variation in the evaluation of blood flow underscore the need to consider the present findings with caution.

CONCLUSION

The studies submitted to the present meta-analysis demonstrate that TENS has several benefits and plays an important role in hemodynamics, exerting a direct effect on increasing blood flow and improving blood pressure.

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