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Effects on hemodynamic variables and echocardiographic parameters after a stellate ganglion block in 15 healthy volunteers

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ABSTRACT

Background: The sympathetic nervous system has an important role in generating pain. Various pathomechanisms are involved that respond well to the application of local anesthetics (LA), for example to the stellate ganglion block (SGB).
Objectives: We wanted to know more about the effects of SGB on cardiovascular parameters.
Methods: We included 15 healthy volunteers; another 15 healthy volunteers as a control group (sham injection of LA). In order to produce a more precise SGB, we employed only a small volume of LA (3 mL), a LA with a lower permeability (procaine 1%), and a modified injection technique. Systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), and echocardiographic parameters were recorded before and after SGB. We also investigated whether there are side differences (left and right SBG).
Results: At baseline all parameters were within the normal range. After performing right and left SGB DBP significantly increased (on the right side from 68.73 ± 8.61 to 73.53 ± 11.10, $p = 0.015$; on the left side from 70.66 ± 13.01 to 77.93 ± 10.40, $p = 0.003$). In the control group no increase in DBP was observed. No side-specific differences were found, except a significant reduction in the maximum velocity of myocardial contraction during the systole with left-sided SGB.
Conclusions: Even with our methods we could not prevent the simultaneous occurrence of a partial parasympatholytic effect. For this reason, the SGB has only minor hemodynamic effects, which is desirable as it enhances the safety of the SGB.

1. Introduction

1.1. Background

The autonomic nervous system plays an important role in the regulation of blood pressure, heart rate, myocardial contractility and coronary perfusion. The balance of activity of its sympathetic and parasympathetic branches has a key part in this (Alston et al., 2011; Drew and Sinoway, 2012; Esler, 2010; Jänig, 2006; Low, 1993; Paton and Spyer, 2013; Schwartz and De Ferrari, 2011; Sunagawa et al., 1998; Yanowitz et al., 1966).

An imbalance in the autonomic cardiac fibers can, for example, lead to cardiac arrhythmias (Lopez-Sendon et al., 2004; Nademanee et al., 2000; Ogawa et al., 2007; Schwartz, 1984; Schwartz, 1998; Schwartz and Zaza, 1986; Shen et al., 2011) or hypertension (Fernandez et al., 2012; Grassi, 2010; Grassi and Seravalle, 2012).

An imbalance of the sympathetic and parasympathetic branches of the autonomic nervous system, however, can also cause and maintain pain and inflammation (Baron, 2006; Baron and Jänig, 1998; Levick et al., 2010; Ricker, 1924; Stanton-Hicks et al., 1995; Straub et al., 2006; Tracey, 2002; Zhang et al., 2009). Here, peripheral and central memory and sensitization processes take place that implicate the sympathetic branch (Jänig and Baron, 2011). Various pathomechanisms are involved that can be influenced by local anesthesia, including, for example the following:

- Long-term potentiation in the sympathetic ganglia (Alkadhi et al., 2005)
- Sympathetic sprouting (Almarestani et al., 2008; Chartier et al., 2014; Chung and Chung, 2002; Docimo et al., 2008; Garcia-Larrea and Magnin,

Abbreviations: DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; IVRT, isovolumetric relaxation time; LA, local anesthetics; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; SD, standard deviation; SG, stellate ganglion; SGB, stellate ganglion block; WDR, wide dynamic range.

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2008; Martinez-Lavin and Solano, 2009; McLachlan et al., 1993; McLachlan and Hu, 2014; Price and Mudge, 1983; Ramer et al., 1999: Yen et al., 2006)
- Sympathetic-afferent coupling (Baron and Jänig, 1998; Baron and Raja, 2002; Devor and Jänig, 1981; Devor et al., 1994; Jänig and Koltzenburg, 1991; Jänig and Koltzenburg, 1992; Jänig and McLachlan, 1994; Jänig et al., 1996; Schattschneider et al., 2003)
- Positive neuronal feedback loops, with the sympathetic nervous system being implicated on a spinal and supraspinal level (Eggli and Fischer, 2011; Fischer, 1998; Fischer, 2003; Fischer, 2013; Jänig, 2011)
- Sensitization of wide dynamic range (WDR) neurons (Zieglgänsberger, 2010)
- Release of pro-inflammatory neuropeptides from sympathetic fibers (Baron and Jänig, 1998; Cassuto et al., 2006; Goadsby and Edvinsson, 1993; Herbert and Holzer, 2002; Jänig, 2006; Miao et al., 1996a; Miao et al., 1996b; Strittmatter et al., 1996; van de Beek et al., 2001)
- Vasomotor-related inflammation (Ricker, 1924; Jänig, 2006)
- Disruption of the interaction between the sympathetic nervous system and the immune system (Elenkov et al., 2000; Hori et al., 1995; Jänig, 2006; Madden and Felten, 1995; Marvar and Harrison, 2012; Pongratz and Straub, 2010; Pongratz et al., 2012; Straub et al., 2006; Watkins et al., 2007; Yokoyama et al., 2000).

Local anesthetics are gaining ground in the treatment of these disorders of the autonomic nervous system. For example, studies have demonstrated that the stellate ganglion block using LA (Gadhinglajkar et al., 2013; Garneau et al., 2011; Huang et al., 2013; Mata Francisco et al., 2013; Nademanee et al., 2000; Patel et al., 2011; Vaseghi et al., 2012) or stellectomy (Schwartz, 1984) have a beneficial effect on cardiac arrhythmias.

Also, LAs can, on the one hand, by exerting an immediate pharmacological effect favorably influence pain and inflammation (Cassuto et al., 2006; Hollmann and Durieux, 2000; Kirillova et al., 2011; Koppert et al., 1998; Pietruck et al., 2003; Ricker, 1924; Spiess, 1906); and, on the other hand, by being delivered to the stellate ganglion favorably influence pain (Kohjitani et al., 2002; Liu et al., 2013; Masuda and Okamoto, 2005; Noma et al., 2013; Peterson et al., 2009; Pfister and Fischer, 2009; Price et al., 1998; Rosenquist and Vrooman, 2013; Salvaggio et al., 2008; Shanthanna, 2013; Wang et al., 2005; Yoo et al., 2012) and inflammation (Liu et al., 2013; Masuda and Okamoto, 2005; Noma et al., 2013; Pfister and Fischer, 2009; Wang et al., 2005; Yoo et al., 2012). The same beneficial effect on pain and inflammation has also been reported for sympathectomy (Leriche, 1958; Noble et al., 2006).

The often longstanding analgesic action of local anesthetics cannot only be explained by their pharmacological effect, but also by various other mechanisms such as, for example, by indirectly reducing long-term potentiation (Kansha et al., 1999; Tan et al., 1999), by decreasing sympathetic sprouting (Chung and Chung, 2001; Takatori et al., 2006; Xie et al., 2007; Zhang et al., 2004), by decreasing the sympathetically mediated activity of WDR neurons (Roberts and Foglesong, 1988), and by temporarily disrupting the positive neuronal feedback loops ("reset") and subsequently re-organizing the systems involved (Fischer, 1998; Jänig, 2011; McQuay and Moore, 1999; Pfister and Fischer, 2009; Rosenquist and Vrooman, 2013).

This is why injections of local anesthetic and the stellate ganglion block are gaining importance, especially in the context of diagnostic and therapeutic local anesthesia (neural therapy) and interventional pain therapy.

Against this background, it is essential to the safety of our patients to gain more insights into the effects of the SGB on cardiovascular parameters. A review of previous work in this field revealed heterogeneous and in part inconsistent results. One possible explanation for these greatly varying results, which we will use as our hypothesis, is that different but always relatively large volumes of LA have been delivered in these studies so that together with the stellate ganglion a varying number of parasympathetic nerves in the vicinity have also been anesthetized. This effect is enhanced by both the diffusion properties of the amide-based LAs (such as lidocaine), which have been primarily administered in previous studies, and by injection techniques where the needle tip comes to rest close to parasympathetic structures.

1.2. Objectives

The first aim of this study was a) to elucidate whether we can generate more conclusive results on the changes in cardiovascular parameters by more accurately targeting the stellate ganglion and by avoiding as many adjacent neuronal structures as possible, and b) to learn whether these changes are the specific result of the SGB or whether they are unspecific.

Our study efforts therefore focused on performing the stellate ganglion block by using

1. the smallest possible volume of local anesthetic;
2. a less permeable local anesthetic;
3. an injection technique employing the largest possible distance between the needle and the parasympathetic structures (as closely as possible to the SG), and
4. a control group (sham injection), recruited subsequently to compare only important (significant) changes (studies on SGB so far, as we found, were conducted without such a control group).

The second objective was to find out whether a difference in cardiovascular parameters can be observed between right and left SGB in the same study participants. The literature search revealed that so far no studies have been published where the same study participants received a bilateral stellate ganglion block and were then monitored by echocardiography: Cinca et al. (1985) and Egawa et al. (2001) performed a bilateral SGB, but conducted electrophysiological instead of echocardiographic examinations (Cinca et al., 1985; Egawa et al., 2001). All other previous studies in the field investigated the effects of injections to the right and left side of the stellate ganglion in different individuals.

2. Methods

2.1. Study participants

The study included 15 healthy volunteers (American Society of Anesthesiologists' Physical Status Classification [ASA PS I]; 12 women, 3 men; mean age 46.0 ± 13.49 years), whose written consent had been obtained. None of the participants took medication that is known for producing effects on the cardiovascular system.

A control group (another 15 healthy volunteers, ASA PS I; 8 women, 7 men; mean age 54.7 ± 14.93 years) received a subcutaneous sham injection into the vicinity of the stellate ganglion (single-blind).

Written informed consent was obtained from all participants. The ethical and scientific commission of IFMANT (International Federation of Medical Associations of Neural Therapy) approved of our study design and measurements. Our study is in full compliance with the statements of the Helsinki Declaration.

2.2. Material

We used procaine 1%, an amino ester-type local anesthetic (which has a lower (membrane) permeability than amide-type LAs such as lidocaine). Procaine has a short duration of action (20 to 30 min), and it is metabolized by the unspecific pseudocholinesterase in nearly every tissue. Its therapeutically active metabolites include *para*-amino benzoic acid (PABA) and diethylaminoethanol (DEAE). Among other things, they produce vasodilation, and they exhibit sealing effects on the capillary walls as well as membrane stabilizing effects. We used a 20 mm × 0.4 mm needle.

2.3. Stellate ganglion block

A special technique was used for the purpose mentioned above (Fischer, 2014). We modified the approach described by Leriche and Fontaine (1934) and Leriche (1958) and Dosch (1986). The operator uses his or her middle finger to palpate the sternocleidomastoid muscle at the junction between its middle and distal third and shift the muscle medioventrally, thus shifting also the neurovascular bundle of the neck lying underneath (common carotid artery, internal jugular vein, vagus nerve) into the same direction, i.e., away from the injection zone. This enables the operator to palpate the anterior tubercle of the transverse process of the sixth cervical vertebra (carotid or Chassaignac's tubercle). Next, the patient's cervical spine is slightly extended and rotated 45 degrees to the contralateral side of the block, with the palpating finger being left on the Chassaignac's tubercle. The point of needle puncture lies 1 mm below Chassaignac's tubercle. The needle is directed 45 degrees caudally, 45 degrees medially and 45 degrees dorsally. The needle is inserted to a depth of no >2 cm. After a negative aspirate for blood and cerebrospinal fluid, 3 mL of procaine 1% were injected. Proper placement of the injection to the stellate ganglion was verified with the presence of ipsilateral Horner's syndrome and the simultaneous rise in the skin temperature of the ipsilateral upper extremity. All SGBs were performed by the same physician (KP).

2.4. Sham injection

In the participants of the control group, who received a sham injection, the same palpation procedure and the same point of needle puncture was used. 3 mL of procaine 1% were then subcutaneously injected dorsal to the sternocleidomastoid muscle. Prior to treatment, the participants of the control group did not know whether they had been assigned to receive a stellate or a subcutaneous injection (single-blind).

2.5. Hemodynamic and echocardiographic measurements and calculations

In addition to systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg), and heart rate (HR; beats per min), echocardiographic parameters were recorded using the General Electric Vivid 7 (with a 3.5 MHz transducer probe).

The left ventricular ejection fraction (LVEF) was measured to assess systolic function: it is calculated from the difference between the left ventricular end-diastolic volume (LVEDV) and the left ventricular end-systolic volume (LVESV) and usually expressed as a percentage:

$$LVEF = LVEDV–LVESV/LVEDV.$$

A tissue Doppler was used to derive the peak systolic myocardial velocity (Sa), as well as the peak early diastolic myocardial relaxation velocity (Ea) and the peak myocardial velocity associated with atrial contraction (Aa). Furthermore, the peak velocities of the early filling wave (wave E; caused by ventricular relaxation) and the left atrial filling wave (wave A; caused by left atrial contraction) were recorded as a measure of mitral inflow.

In addition, we recorded another parameter of left ventricular diastolic function, i.e., the isovolumetric relaxation time (IVRT).

All hemodynamic measurements were performed by the same cardiologist (MG) with many years of experience in this field.

In the control group, the comparison was restricted to the pre- and post-injection DBP values which were increased in the treatment group.

2.6. Study protocol

On day 1, all study participants received an injection to the right SG; on day 2, the same procedure was repeated on the left side. At baseline, i.e., a few minutes prior to each injection, both hemodynamic and echocardiographic measurements were conducted. The same parameters were recorded approx. 4 min after the injection in the presence of Horner's syndrome.

In the control group (see Section 2.4) we injected to the right side in 7, and to the left side in 8 study participants. Their diastolic blood pressure (see Discussion) was measured a few minutes before and 4 min after the injection.

2.7. Statistical analysis

The data are presented as means (±standard deviation, SD). Statistical significance was defined in terms of p values < 0.05. Hemodynamic and echocardiographic values were analyzed using the non-parametric Wilcoxon test to evaluate the difference between paired samples, and the U of Mann-Whitney test statistic was employed to compare the mean values of the left and the right side.

Statistical analysis of the DBP values in the control group was conducted using the Wilcoxon-Mann-Whitney test (p values < 0.05) and the paired t-test (p values < 0.05).

3. Results

Baseline (prior to SGB) levels of heart rate and blood pressure (SBP and DBP) were within normal ranges in all study participants. Following both right and left SGB a significant increase in DBP was observed (right side injection: from 68.73 ± 8.61 mm Hg to 73.53 ± 11.10 mm Hg, $p = 0.015$ [Table 1]; left side injection: from 70.66 ± 13.01 mm Hg to 77.93 ± 10.40 mm Hg, $p = 0.003$ [Table 2]). No significant changes occurred in SBP and HR after both right- and left-sided SGB (Tables 1 and 2).

Compared to baseline, the right SGB did not produce a significant change in the parameters of left-ventricular contractile strength (ejection fraction and myocardial systolic velocity, Sa). With left SGB there was also no change in EF, whereas the Sa wave velocity significantly decreased from 15.46 ± 4.03 cm/s to 13.40 ± 3.46 cm/s ($p = 0.017$).

Concerning the parameters of diastolic function, no statistically significant differences were found between right and left SGB. Also, no side differences were observed after right and left SGB in the same individuals (Table 3). Comparing the difference in means of the hemodynamic parameters (HF, SBP, DBP) we found no difference in either EF or the parameters of diastolic function. However, there was a difference in left ventricular contraction (Sa wave) between the two sides

Table 1
Hemodynamic and echocardiographic parameters before and after right-side SGB (n = 15).

	Baseline values[a] (n = 15)	Values after right-side SGB[a] (n = 15)	p
Hemodynamic parameters			
Arterial SBP (mm Hg)	118.20 ± 16.91	119.13 ± 18.53	0.825
Arterial DBP (mm Hg)	68.73 ± 8.61	73.53 ± 11.10	0.015
HR (bpm)	71.93 ± 6.50	70.46 ± 8.53	0.319
Systolic function			
LVEF (%)	68.06 ± 5.31	67.06 ± 4.71	0.529
Doppler Sa (cm/s)	15.00 ± 4.08	15.53 ± 3.79	0.550
Diastolic function			
E wave (m/s)	0.79 ± 0.25	0.75 ± 0.26	0.378
A wave (m/s)	0.59 ± 0.32	0.59 ± 0.34	0.925
Doppler Ea (cm/s)	24.80 ± 7.63	22.26 ± 5.02	0.176
Doppler Aa (cm/s)	16.86 ± 5.84	19.46 ± 5.37	0.082
E/A ratio	0.03 ± 0.01	0.03 ± 0.02	0.477
IVRT (ms)	85.73 ± 17.90	88.40 ± 17.03	0.932

DBP: diastolic blood pressure; Doppler Aa: peak myocardial velocity during atrial contraction; Doppler Ea: peak early diastolic velocity during myocardial relaxation; Doppler Sa: peak systolic velocity during myocardial contraction; HR: heart rate; IVRT: isovolumetric relaxation time; SBP: systolic blood pressure; SGB: stellate ganglion block; A wave: peak blood flow velocity during late diastolic filling (due to atrial contraction); E wave: peak blood flow velocity during early diastolic filling; cm: centimeters; s: second; m: meters; ms: milliseconds.

[a] Mean ± SD.

Table 2
Hemodynamic variables and echocardiographic findings prior to and after left-side SGB (n = 15).

	Baseline values[a] (n = 15)	Values after left-side SGB[a] (n = 15)	p
Hemodynamic variables			
Arterial SBP (mm Hg)	119.06 ± 17.87	122.37 ± 18.99	0.292
Arterial DBP (mm Hg)	70.66 ± 13.01	77.93 ± 10.40	0.003
HR (bpm)	71.60 ± 7.22	70.40 ± 6.25	0.800
Systolic function			
LVEF (%)	64.86 ± 6.10	65.73 ± 5.84	0.479
Doppler Sa (cm/s)	15.46 ± 4.03	13.40 ± 3.46	0.017
Diastolic function			
E wave (m/s)	0.75 ± 0.27	0.74 ± 0.28	0.700
A wave (m/s)	0.59 ± 0.30	0.62 ± 0.37	0.154
Doppler Ea (cm/s)	22.53 ± 8.18	20.73 ± 7.15	0.251
Doppler Aa (cm/s)	15.73 ± 4.92	15.60 ± 5.36	0.384
E/A ratio	0.03 ± 0.02	0.04 ± 0.02	0.394
IVRT (ms)	85.73 ± 17.90	88.73 ± 17.03	0.462

DBP: diastolic blood pressure; Doppler Aa: peak myocardial velocity during atrial contraction; Doppler Ea: peak early diastolic velocity during myocardial relaxation; Doppler Sa: peak systolic velocity during myocardial contraction; HR: heart rate; IVRT: isovolumetric relaxation time; SBP: systolic blood pressure; SGB: stellate ganglion block; A wave: peak blood flow velocity during late diastolic filling (due to atrial contraction); E wave: peak blood flow velocity during early diastolic filling; cm: centimeters; s: second; m: meters; ms: milliseconds.
[a] Mean ± SD.

(difference in means for left SGB: 2.06 ± 2.84 cm/s and difference in means for right SGB: 0.53 ± 2.61 cm/s; $p = 0.021$).

Apart from a mild, transient (lasting a few minutes) dizziness, no other side effects or complications occurred.

In the control group, the participants' diastolic blood pressure did not increase before or after the injection ($p = 0.230$ and $p = 0.283$, respectively).

4. Discussion

Previous studies investigating the stellate ganglion block (SGB) have produced variable results regarding:

- *Blood pressure*
  Blood pressure elevations following left and right SGB were reported by Kweon et al. (2006; for DBP and SBP) as well as Park et al. (2010; only mean blood pressure readings were documented). No changes in either DBP or SBP were found by Goh et al. (1990) and Lobato et al. (2000).
- *Heart rate*
  With right-side SGB, the heart rate was either decreased (Egawa et al., 2001; Goh et al., 1990; Kashima et al., 1981; Park et al., 2010; Rogers et al., 1978), unchanged (Fujiki et al., 1999; Kim et al., 2010; Lobato et al., 2000), or increased (Kweon et al., 2006). With left-side SGB the heart rate was either decreased (Egawa et al., 2001), unchanged (Fujiki et al., 1999; Garneau et al., 2011; Goh et al., 1990; Kashima et al., 1981; Kim et al., 2010; Lobato et al., 2000; Rogers et al., 1978; Ogawa et al., 2007), or increased (Kweon et al., 2006; Park et al., 2010).
- *Ventricular function (echocardiography)*
  No change in ejection fraction (EF) was observed with right-side SGB (Gardner et al., 1993; Garneau et al., 2011; Lobato et al., 2000). With left-side SGB, there have been reports of increased left ventricular end-diastolic and end-systolic volumes (Lobato et al., 2000), reduced contractility (Milne et al., 1982), a reduction in afterload, an increased stroke volume as well as a prolonged isovolumetric relaxation period (Schlack and Dinter, 2000).

Table 3
Differences in post-SGB changes of hemodynamic and echocardiographic parameters between left and right nerve block (n = 15).

	Change left[a] (n = 15)	Change right[a] (n = 15)	p
Hemodynamic variables			
Arterial SBP (mm Hg)	3.66 ± 10.86	0.93 ± 9.30	0.394
Arterial DBP (mm Hg)	7.26 ± 7.71	4.80 ± 6.95	0.329
HR (bpm)	−1.2 ± 7.90	−1.92 ± 6.18	0.456
Systolic function			
LVEF (%)	0.86 ± 3.72	−1.00 ± 6.41	0.426
Doppler Sa (cm/s)	−2.06 ± 2.84	0.53 ± 2.61	0.021
Diastolic function			
E wave (m/s)	0.001 ± 0.08	−0.03 ± 0.12	0.289
A wave (m/s)	0.03 ± 0.09	0.003 ± 0.07	0.503
Doppler Ea (cm/s)	−1.80 ± 4.66	−2.53 ± 6.82	0.560
Doppler Aa (cm/s)	−0.13 ± 4.29	2.33 ± 5.19	0.203
E/A ratio	0.001 ± 0.007	0.0006 ± 0.01	0.309
IVRT (ms)	2.66 ± 14.28	1.60 ± 15.80	0.519

DBP: diastolic blood pressure; Doppler Aa: peak myocardial velocity during atrial contraction; Doppler Ea: peak early diastolic velocity during myocardial relaxation; Doppler Sa: peak systolic velocity during myocardial contraction; HR: heart rate; IVRT: isovolumetric relaxation time; SBP: systolic blood pressure; SGB: stellate ganglion block; A wave: peak blood flow velocity during late diastolic filling (due to atrial contraction); E wave: peak blood flow velocity during early diastolic filling; cm: centimeters; s: second; m: meters; ms: milliseconds.
[a] Mean ± SD.

Heterogeneous results have also been published for a variety of other parameters that were not recorded in our study, including heart rate variability after right or left SGB (Fujiki et al., 1999; Kim et al., 2010; Kweon et al., 2006; Taneyama and Goto, 2009). Different findings have also been revealed regarding the electrocardiographically documented QT interval (prolongation, shortening or no change) following right- and/or left-side SGB (Cinca et al., 1985; Egawa et al., 2001; Fujii et al., 2004; Gardner et al., 1993; Garneau et al., 2011; Kashima et al., 1981; Milne et al., 1982; Rogers et al., 1973; Saxena et al., 2004; Solti et al., 1978; Wong and Wang, 1999; Yanowitz et al., 1966).

From our point of view, the markedly different findings obtained in the various previous studies are related to the fact that these studies exclusively used highly permeable LAs of different, but in all cases relatively large volumes (5–15 mL), leading to the blockade of not only sympathetic but parasympathetic nerve fibers as well. Moreover, different injection techniques were used in these studies. As a result, the SGB injections produced a variable spread of the LA, and thus included a variable number of sympathetic fibers of the sympathetic trunk and, at the same time, a variable number of parasympathetic nerve fibers as well.

Despite the otherwise heterogeneous results of previous studies, there is some trend indicating that the right stellate ganglion fibers are responsible for heart rate control (sinuatrial node), while the left stellate ganglion fibers supply the ventricles (coronary vessels, myocardium; Fujiki et al., 1999; Rogers et al., 1973; Schwartz, 1984; Song et al., 2009; Vaseghi et al., 2012).

This is consistent with the fact that we found a significant decrease in Sa velocity after left SGB (Table 2), which is also compatible with the increase in LVEF observed after stimulation of the left SG (Wong and Wang, 1999). Otherwise, there were no side differences following right and left SGB.

The majority of studies did not find the same significant increase in DBP after right and left SGB that we measured in our study, except Kweon et al. Interestingly, the significant increase of DBP in their study can be traced back to using relatively small volumes of LA (compared to the volumes injected in most of the other studies; Kweon et al., 2006). This discrepancy cannot be easily explained since we do not know exactly which sympathetic and parasympathetic nerve fibers (Fig. 1) have been blocked by the LA. And given the anatomic variability and the complex network of the thin afferent and efferent sympathetic cardiac nerves and the parasympathetic superior and inferior cervical cardiac branches (Fig. 2), it cannot be readily elicited by contrast-enhanced imaging techniques either, even though the spread of the

local anesthetic following SGB has been visualized by ultrasound (Kapral et al., 1995), magnetic resonance imaging (MRI; Hogan et al., 1992), computerized tomography (CT; Feigl et al., 2007), and latex injections (Honma et al., 2000).

Furthermore, the regulation of DBP is a complex process. Among other factors, the DBP is related to the peripheral vascular resistance. Depending on their concentration and receptor (tissue-specific), norepinephrine and epinephrine can either constrict or dilate the resistance vessels. The same applies to NO, O_2, CO_2, lactate, K^+, endothelin, serotonin etc. (Burnstock, 2012; Lombard and Cowley, 2012). Some of these substances are perfusion-dependent, and the perfusion is also altered after SGB. Thus, a feedback mechanism might be involved.

Since an obvious explanation was lacking we wondered whether the mental stress that study participants suffered during the injection might have a role in increasing the DBP. Another theoretical possibility would be a pharmacological effect of procaine (almost all other studies used amid-type LAa). Thus, a control group (sham injection) was added to exclude these two possibilities.

We informed the participants in the control group that we would either perform a stellate ganglion block or just a subcutaneous injection close to the stellate ganglion. This sham injection included the same volume of procaine, the sensation of pinprick in the same anatomical region and the palpation of the stellate ganglion (which we performed in identical fashion in the two groups). Both true and sham injections evoke the same kind of anticipation (that is, the study participants would have to reckon with an injection). Since the diastolic blood pressure readings before and after the injection were unchanged in these study participants, we may safely assume that the increase in DBP in the SGB treatment group is the specific result of the stellate ganglion block in our study.

In our opinion, the complex anatomy of the stellate ganglion and its connections, which is concentrated in a very small area, inhibits an exclusive nerve block of just the sympathetic structures (despite the small volumes of slowly diffusing LA and the special injection technique that we used in our experiment), and hence the interpretation of the findings.

The sympathetic and the parasympathetic nerves merge at the cardiac plexus (Fig. 1; Clara, 1959; Janes et al., 1986; Jänig, 2006; Kawashima, 2005; Samandari, 1994; Sinelnikov, 1981). The parasympathetic fibers mainly originate from the recurrent nerve and the cervical vagus nerve. However, the cardiac nerves (i.e., the superior, middle and

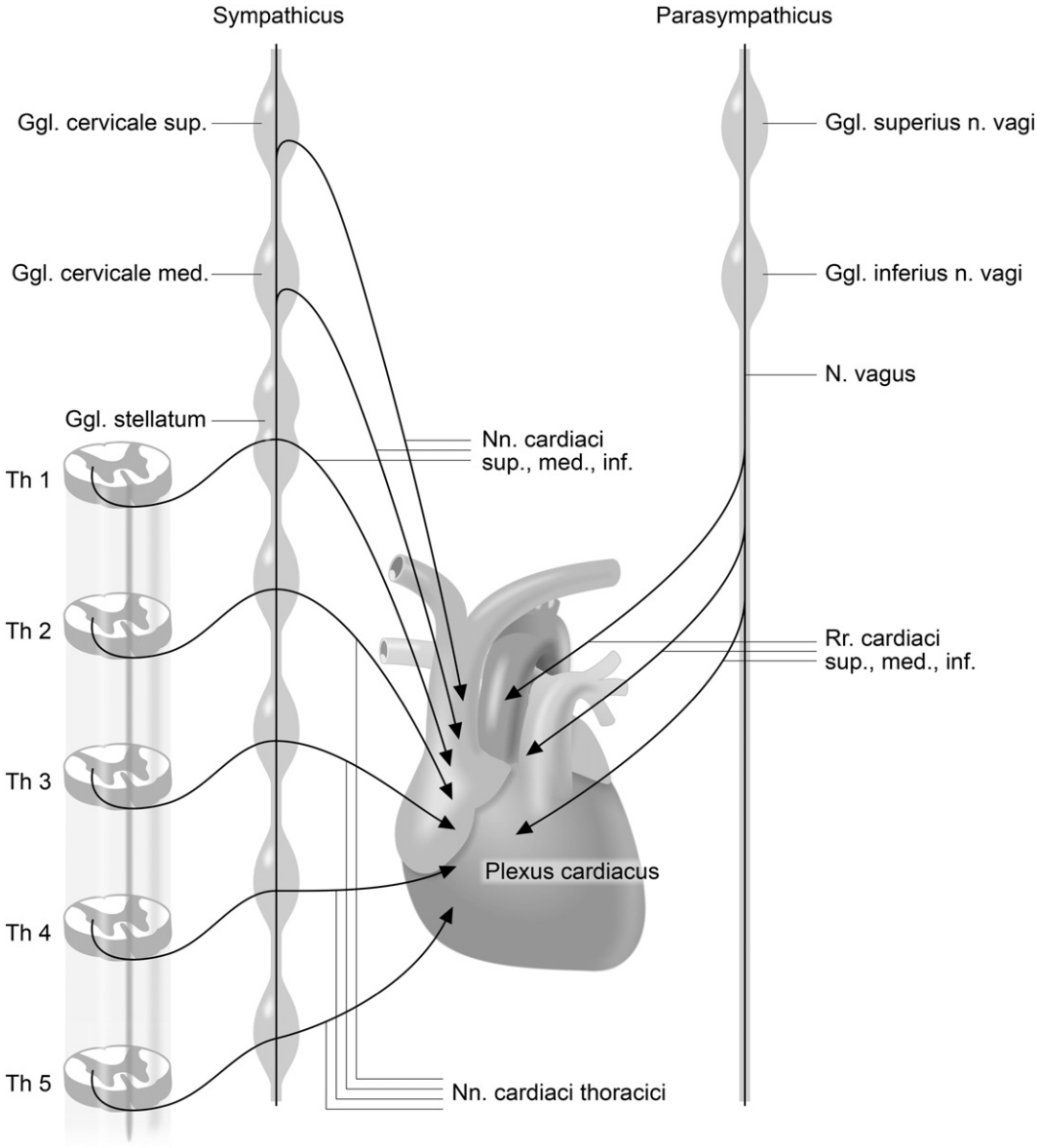
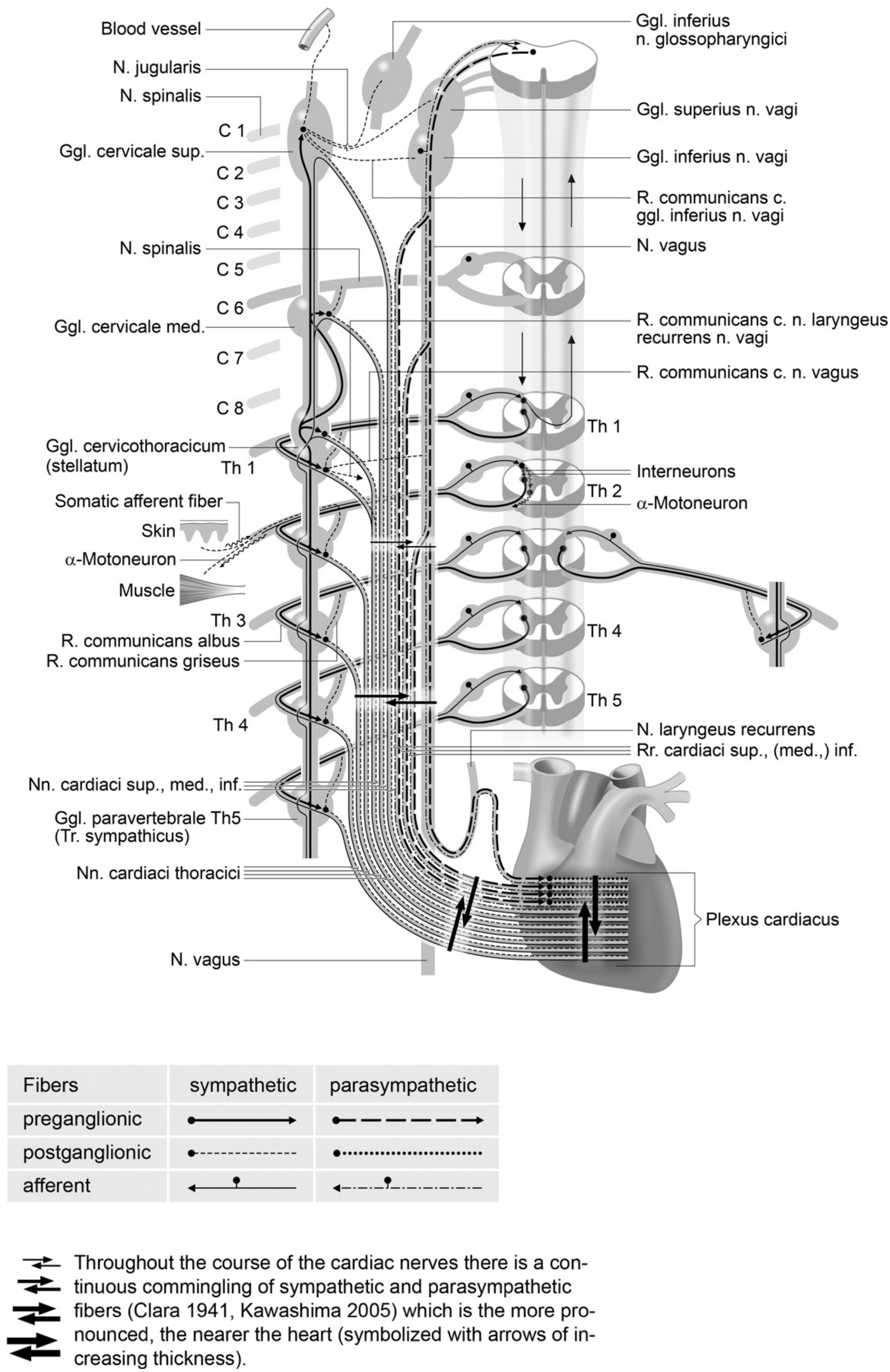


Fig. 1. Diagram showing the autonomic input to the cardiac plexus. For clarity of presentation, the spinal cord is displayed on the side rather than in the middle. The thoracic cardiac nerves travel to the cardiac plexus, independently of the cervical ganglia, and are not affected by stellate ganglion block.

inferior cervical cardiac nerves and the superior, medial and inferior cervical cardiac branches [Fig. 2]) contain both sympathetic and parasympathetic fibers, even in their more proximal portions (Clara, 1959; Kawashima, 2005). Moreover, there are large individual differences in the composition and number of cardiac fibers; the reason is that the sympathetic cardiac nerves soon after their origin can carry



parasympathetic fibers from the vagus nerve and, vice versa, the parasympathetic cervical cardiac branches can carry sympathetic fibers (Fig. 2; Clara, 1959).

In addition, there are larger, defined interconnections between the sympathetic and the parasympathetic branches, such as, for example, the jugular nerve connecting the superior cervical ganglia and the vagus nerve (Fig. 2). Even if we very specifically targeted the stellate ganglion, the nerve block would interrupt the fibers traveling to the superior cervical ganglia and thus the jugular nerve activity. Other connections from the sympathetic to the parasympathetic branch include the communicating branches to the vagus nerve and to the recurrent laryngeal nerve, both of which arise from the stellate ganglion (Fig. 2; Clara, 1959; Sinelnikov, 1981). Thus, the injection of a local anesthetic into sympathetic nerve tissue will at the same time automatically produce a partial block of parasympathetic components.

The sympathetic regulation of the heart is not the sole responsibility of the cervical ganglia (i.e., inferior [stellate ganglion], middle cervical ganglion and superior cervical ganglion): Janes et al. described sympathetic mediastinal ganglia that are also contributing to cardiac regulation. Sympathetic fibers arising from the ganglia T2 to T5 of the paravertebral chain are directly destined to the heart and join the cardiac plexus (thoracic cardiac nerves), without making a "detour" via the cervical ganglia (Fig. 1; Clara, 1959; Janes et al., 1986; Kawashima, 2005; Samandari, 1994; Sinelnikov, 1981; Song et al., 2009). And even after a cervical ganglion block, these will remain active. Hence, the sympathetic fibers extending down to the heart will not be completely blocked by applying a local anesthetic to the cervical ganglia. In our opinion, the same considerations also apply to stellate ganglionectomy (Leriche, 1958; Xie et al., 2011; Yoshimoto et al., 2008).

For all these reasons, the balance between the sympathetic and parasympathetic divisions of the autonomic nervous system is hardly disrupted by stellate ganglion injections. Otherwise, we would expect the changes in cardiovascular parameters, which occur as a result of the theoretically isolated elimination of sympathetic cardiac fibers, to be much more pronounced.

5. Limitations

Sympathetic and parasympathetic activity within the cardiovascular system also goes along with changes of heart rate variability. By addressing the heart rate variability (using spectral analysis), we could have possibly made additional statements about sympathetic and parasympathetic activity after SGB.

Another limitation is the fact that we performed the right and left SGB in the same sequence in all subjects (on day 1, all study participants received an injection to the right SG; on day 2, the same procedure was repeated on the left side). As a result, a potential leftover effect, or subjects' anticipation of effect, may have influenced the results.

6. Conclusions

The heterogeneous results concerning the hemodynamic parameters following SGB that were observed in several studies can be attributed to:

1. Different injection techniques,
2. Different injection volumes,
3. Different diffusion properties of the various LAs administered;
4. Anatomical variability and different baseline values for the sympathetic and parasympathetic tones (which gain more significance with single-case reports or small numbers of study participants).

But even the precise infiltration of the stellate ganglion (special injection technique) with a small volume of procaine (a local anesthetic that is known for its low permeability) that we used in our study cannot avoid a partial parasympathicolytic effect. Also, there are sympathetic fibers from the thoracic segments lying inferiorly to the stellate ganglion that travel to the heart directly and that are unaffected by small-volume injections of LA.

For these reasons, the hemodynamic effects are negligible. This does not mean though that the therapeutic effects following from SGB are diminished since the simultaneous anesthesia of parasympathetic fibers will not impair the beneficial antiarrhythmic and pain inhibiting effects (it may even have a synergistic effect).

Although some changes in hemodynamic and echocardiographic parameters following SGB meet the level of statistical significance, they do not have any clinical significance.

In conclusion, the SGB is safe to the cardiovascular system, and there are hardly any contraindications to the application of small volumes (3–5 mL) of procaine 1%. From the researcher's point of view we will have to accept though that isolated sympatholysis is not possible with stellate ganglion block.

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Fig. 2. A greatly simplified schematic representation of the autonomic efferent and afferent innervation of the heart, adapted from various sources (Clara, 1959; Gilman, 2007; Janes et al., 1986; Jänig, 2006; Kawashima, 2005; Lanz and Wachsmith, 2004; Mathias and Bannister, 2013; Netter, 1994; Robertson et al., 2012; Rohen, 2001; Samandari, 1994; Schiebler and Korf, 2007; Sinelnikov, 1981; Thomas and Gerdisch, 1990; Trepel, 2012; Waldeyer and Mayet, 1993; Williams and Bannister, 1995; Wilson Pauwels et al., 1997). Note the close proximity of sympathetic and parasympathetic fibers. Soon after their origin, the sympathetic cardiac nerve fibers can carry parasympathetic fibers, and vice versa, the parasympathetic cervical cardiac branches can carry sympathetic fibers (Clara, 1959; Kawashima, 2005). Other connections between the sympathetic and the parasympathetic divisions include the rami communicantes (for example, the jugular nerve, and branches arising from the stellate ganglion and connecting it with the vagus nerve and the recurrent laryngeal nerve; Clara, 1959; Sinelnikov, 1981). Note: The number and course of the cardiac nerves and rami can vary across individuals, and this is reflected by the partly inconsistent terminology in the literature. For example, some of the references do not mention the ramus cardiacus medius (the middle cervical cardiac ramus). The diagram is intended to illustrate how parasympathetic fibers can be (inadvertently) affected by SGB along with the SGB's sympathetic targets.

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