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# Asserted and neglected issues linking evidence-based and Chinese medicines for cardiac rehabilitation

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## Abstract

High blood pressure is among the most prevalent chronic disease in adults that impacts on the quality of life of patients, which are often subjected to physical rehabilitation. Chinese medicine intervention in patients with hypertension presents promising albeit inconclusive results, mostly due to methodological issues. This paper discusses asserted and neglected issues linking evidence-based and Chinese medicines as related to systemic arterial hypertension, as well as their impact on the physical rehabilitation of those patients. On the one hand, natural history of hypertension, pulse palpation, and herbal therapy are among the asserted issues because of the scientific evidence collected about them, either in favor or against its integration to the current medical practice. On the other hand, anatomical variations of vessels and comparative physiology are among the most commonly neglected issues because previous researches on integrative medicine ignored the possible effects of these issues as related to the study's outcome. The asserted issues highlighted in this paper

stimulate the increasing use of Chinese medicine for health care and the continuity of research on integrative medicine in the cardiovascular field for rehabilitation. The neglected issues poses additional challenges that must not be overlooked in future research on this topic so that the integration of both traditional and current knowledge may be of benefit to the population with cardiovascular disease.

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**Key words:** Cardiovascular disease; Hypertension; Chinese medicine; Rehabilitation; Integrative medicine

**Core tip:** Integrative medicine might provide better clinical results than evidence-based or Chinese medicines isolated for patients undergoing cardiac rehabilitation. The asserted issues highlighted in this paper (natural history of hypertension, pulse palpation, and herbal therapy) stimulate the increasing use of Chinese medicine for health care and the continuity of research on integrative medicine in the cardiovascular field. Conversely, some neglected issues (anatomical variations of vessels and comparative physiology) poses challenges that must not be overlooked in future research on this topic so that the integration of both traditional and current knowledge may be of benefit to the population with cardiovascular diseases.

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## INTRODUCTION

High blood pressure is a major public health problem

worldwide. Hypertension is among the most prevalent chronic, non-contagious disease in adults<sup>[1]</sup>, despite the trend to decrease its prevalence in some countries<sup>[2]</sup>. The natural history of this disease still needs elucidation: although most of its modifiable and non-modifiable risk factors are well known, the etiology of primary systemic arterial hypertension (SAH) remains uncertain<sup>[3]</sup>. The long-term impact of hypertension on health is nevertheless evident. Small, middle and large-sized arteries are the earliest body structures affected by time-sustained levels of high blood pressure<sup>[4]</sup>. Such arterial remodeling process contributes to the pathophysiology of this condition in target-organs others than the arteries such as the skeletal muscle<sup>[5]</sup>, heart, kidneys, brain, and eyes<sup>[6]</sup>. Without early and proper intervention, organic functions start to deteriorate such that they are detectable by either laboratorial or imaging exams as a complement to the clinical examination of signs and symptoms<sup>[3]</sup>. On a timely fashion, functional capacity may be compromised at the systemic level<sup>[7]</sup> with possible impacts on the quality of life of these patients<sup>[8]</sup>, which often are subjected to physiotherapy and cardiac rehabilitation.

Chinese medicine comprises a phenomenological, philosophic, and systematic traditional health care system developed through almost five millennia<sup>[9]</sup>. Because Chinese medicine was rooted in a sociocultural environment that differed from the European medicine at its early beginning, it is reasonable to expect differences on both medical practices and respective evolution of medical theories. Nevertheless, recent randomized clinical trials, systematic reviews, and meta-analyses on the efficacy of Chinese medicine interventions in patients with SAH were conducted<sup>[10]</sup> with promising albeit inconclusive results. In general, those studies help answering questions raised from the clinical point-of-view, such as “Is Chinese medicine intervention effective for reducing or controlling blood pressure levels”. Investigating this point-of-view leaves opened the traditional point-of-view, which raised questions such as “Are there actual subtypes of hypertension as related to Chinese medicine” or “Is the theory of pattern differentiation for diagnosis relevant for guidance on therapeutic intervention”.

In other words, one may argue what are the scientific evidences for the statements found in the Chinese medicine literature, specially the most antique ones. On the one hand, diving into the traditional Chinese medical literature one can find a number of traditional assertions calling for scientific evidence, if any. On the other hand, researchers often assume that some of these traditional factors may not have a detectable effect on their study's outcome. As it was argued that integrative medicine might provide better clinical results than either one isolated<sup>[11]</sup>, a comprehensive overview of the asserted and neglected issues between evidence-based and Chinese medicines is necessary for both clinicians and researchers. Therefore, this paper discusses the asserted and neglected issues linking evidence-based and Chinese medicines as related to SAH, as well as their possible impact on the physical rehabilitation of those patients.

## ASSERTED ISSUES

In this section, the natural history of SAH, pulse palpation, and herbal therapy are discussed. These topics are considered as asserted issues because of the scientific evidence collected either in favor or against their integration into the current medical practice. However, they should not be considered as final positions because there are lacunas that still need to be addressed in future studies. Table 1 presents summary information about the studies cited in this section.

### Natural history of SAH

The epidemiological concept of natural history of diseases also applies to Chinese medicine, with proper correspondence due to their inherent conceptual differences. The Chinese medicine counterpart of an ongoing morbid process is called *zheng* or pattern. It is worth noticing that a pattern encompasses other information than just signs and symptoms in the Western sense: behavior, emotional states, self-awareness of social status, and physical constitution are among other manifestations considered for diagnosis or “pattern differentiation”<sup>[9]</sup>. Regardless of these differences, Chinese medicine theory presents basic elements of the natural history of diseases such as the existence of protection and risk factors for patterns, a clinical horizon for the onset of manifestations, and health outcomes such as cure, permanent or temporarily disability, and death.

As a matter of fact, there is evidence supporting that most clinical manifestations observed in patients with SAH and that are used for pattern differentiation are actually associated with target-organs damage (TOD). For instance, the clinical manifestations of cerebrovascular disease are strongly associated (Pearson correlation coefficient = 0.718,  $P < 0.001$ ) to those of “Obstruction of phlegm and dampness of Heart/Liver/Gallbladder”<sup>[12]</sup>. Moreover, long-term SAH can lead to myocardial ischemia, conduction defects, arrhythmias, and ventricular hypertrophy<sup>[13]</sup>. The brain is another target-organ usually damaged by the SAH; cognitive disturbances in the elderly are, at least in part, hypertension-related<sup>[14-16]</sup>. High risk of stroke, cognitive decline, and dementia are also associated to SAH<sup>[17-19]</sup>. Some mild retinal changes are largely non-specific except in young patients, hemorrhages, exudates and papilledema, are only present in severe hypertension and are associated with increased cardiovascular risk<sup>[3]</sup>. All the above-cited TOD eventually manifests signs and symptoms, which should be early detected in the natural history of SAH. Therefore, it is possible to assert that there is a relationship between Chinese medicine patterns and the clinical presentation of SAH-including its related comorbidities.

Most importantly, it is also possible to infer that patients with SAH are candidates for cardiac rehabilitation, even from the traditional Chinese medicine point-of-view. Recent systematic reviews found that Chinese medicine mind-body exercises such as *qigong*<sup>[20]</sup> and *taijiquan*<sup>[21]</sup> can be of benefit for patients undergoing antihypertensive

**Table 1** Summary description of studies on the asserted issues linking evidence-based and Chinese medicines

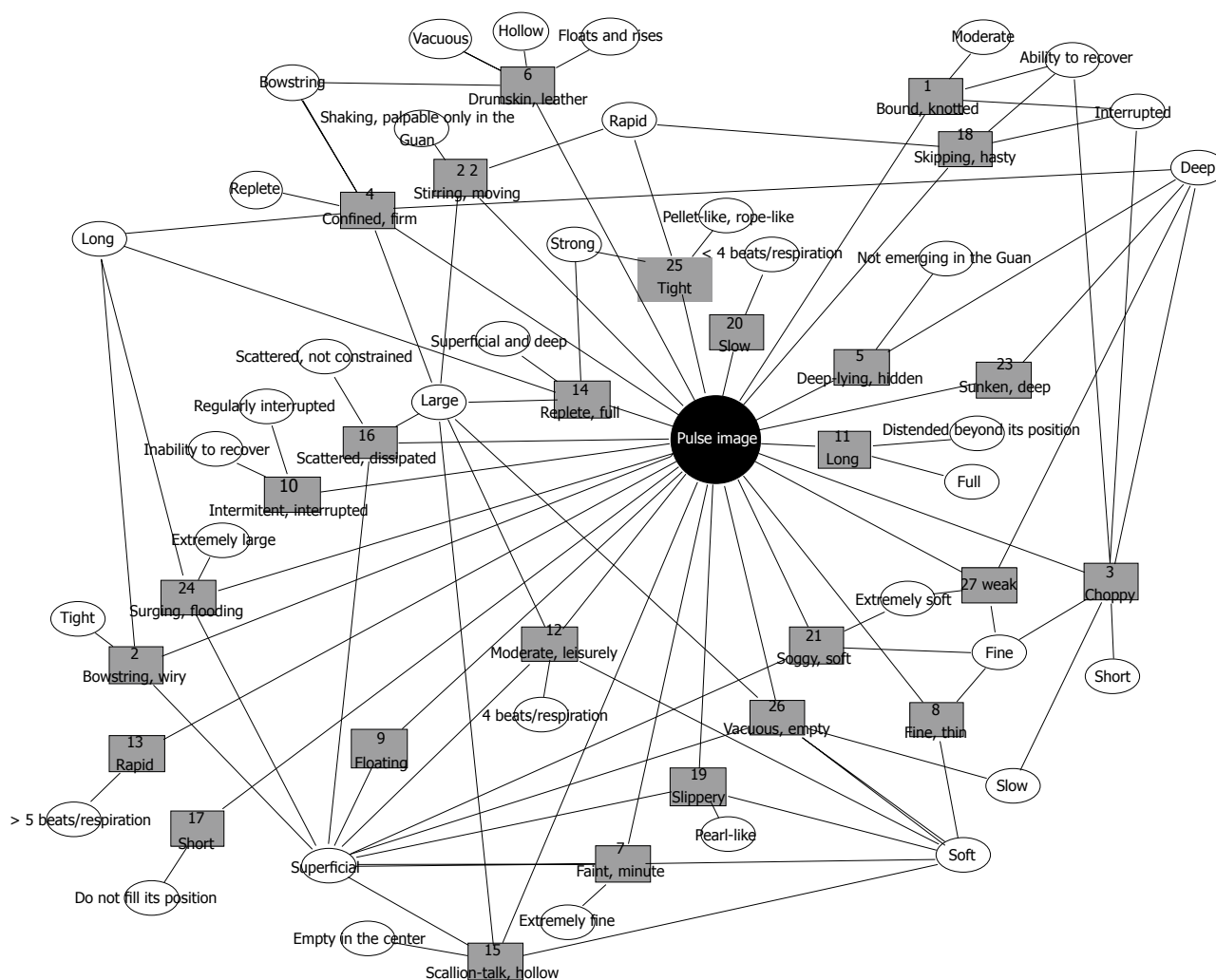
Ref.	Study characteristics	Main results	Main limitation
Natural history of patterns			
Luiz <i>et al</i> <sup>[12]</sup>	Cross-sectional observational design Forty-three patients with hypertension grades I, II and III	Patterns were strongly or moderately associated with target-organ damage Manifestations were at most weakly associated with hemodynamic variables	Target-organ damages were not confirmed by laboratory or imagery methods Patients were under antihypertensive drug therapy
Chan <i>et al</i> <sup>[20]</sup>	Systematic review (8 studies) Seven randomized controlled trials and one non-randomized controlled clinical trial	Qigong improved physical symptoms in patients with coronary artery disease Qigong improved functional capacity of cardiac patients Qigong reduced blood pressure levels No adverse effects reported	Overall poor quality of most studies included in the review Study heterogeneity
Yeh <i>et al</i> <sup>[21]</sup>	Systematic review (26 studies) Nine randomized controlled trials, thirteen non-randomized controlled trials, and four observational studies	<i>Taijiqian</i> reduced blood pressure levels No adverse effects reported	Overall poor quality of most Chinese studies included in the review Study heterogeneity
Pulse palpation			
Luiz <i>et al</i> <sup>[12]</sup>	Cross-sectional observational design Forty-three patients with hypertension grades I, II and III	Frequency analysis of clinical manifestations and pulse images of patterns Most frequent pulse image: wiry pulse (52% of the cases)	Patients were under antihypertensive drug therapy
Ferreira <i>et al</i> <sup>[25]</sup>	Cross-sectional observational study Twenty-nine healthy subjects and twenty-three patients with hypertension grades I, II or III	Higher pulse wave velocity and lower arterial compliance of the brachial-radial artery segment in hypertension	Arterial tonometry was subjected to transducer set-up and manual positioning Patients were under antihypertensive drug therapy
Ferreira <i>et al</i> <sup>[26]</sup>	Cross-sectional observational study Sixty-three healthy subjects and fifty-two patients with hypertension grades I, II or III	Lower arterial compliance of the brachial-radial artery segment in hypertension Hypertrophic remodeling of medium-sized arteries in hypertension	Arterial tonometry was subjected to transducer set-up and manual positioning Patients were under antihypertensive drug therapy
Ferreira <i>et al</i> <sup>[27]</sup>	Cross-sectional observational study Sixty-three healthy subjects and fifty-two patients with hypertension grades I, II or III	Impaired flow-mediated vasodilation in hypertension	Arterial tonometry was subjected to transducer set-up and manual positioning Patients were under antihypertensive drug therapy
Ferreira <i>et al</i> <sup>[28]</sup>	Cross-sectional observational study Sixty-three healthy subjects and fifty-two patients with hypertension grades I, II or III	Increased peripheral vascular resistance immediately after ischemic occlusion Slower response to flow-mediated vasodilation	Arterial tonometry was subjected to transducer set-up and manual positioning Patients were under antihypertensive drug therapy
Lu <sup>[29]</sup>	Cross-sectional observational study Fifty-nine patients with hypertension grades I, II or III	Higher amplitudes for harmonics #0 (heart), #1 (liver), #3 (spleen), #4 (lung), and #6 (gallbladder) in hypertension	Poor description of the studied sample Patients were under antihypertensive drug therapy
Ferreira <sup>[30]</sup>	Computational simulation study Model of the radial artery during "simultaneous pressing"	Lack of correspondence between pressure pulse spectral harmonics and Chinese medicine theory of pulse palpation	No experimental data from patients with hypertension
Herbal therapy			
Xiong <i>et al</i> <sup>[32]</sup>	Narrative review	Herbal therapy may potentially reduce blood pressure variability, inhibit sympathetic activity, prevent target-organ damage, and improve insulin resistance	Potentially biased (selection and report bias) Some results outcome from animal studies not yet tested in humans

treatment. The benefits of *qigong* practice may include the alleviation of physical symptoms related to cardiovascular disease (CVD) (*e.g.*, 63% of the group presented relieving of coronary artery disease symptoms) and the control of blood pressure (*e.g.*, 88% of the group presented lower blood pressure levels) after 1-year practice, and the increase in functional capacity (*e.g.*, 13.7% higher six-minute walk distance after a 16-wk *qigong* training program)<sup>[20]</sup>. Likewise, the benefits of *taijiqian* practice may include a reduction in systolic and diastolic blood pressures (3-32 mmHg and 2-18 mmHg, respectively)<sup>[21]</sup>. However, it is

not clear whether the effects on blood pressure are due to the traditional aspects of Chinese medicine practice or to the increased physical activity itself, or both. Nevertheless, further research is necessary to determine whether Chinese medicine therapy indicated from pattern differentiation is of benefit to patients with SAH, either at secondary or tertiary level of prevention.

### Pulse palpation

Clinical examination in Chinese medicine is not different from that practiced in evidence-based medicine: inspec-



**Figure 1 Pulse image network.** The classic pathologic 27 pulse images (greyish, rectangular nodes) described by common attributes (whitish, ellipsoid nodes) derived from categories (frequency, rhythm, wideness, depth, and qualities). Notice that there are pulse images described by exclusive attributes, while other pulse images are described by shared attributes.

tion, auscultation and olfaction, inquiry and palpation. The most striking difference is that even today Chinese medicine health providers do not make use of any complementary exam or equipment (e.g., arterial tonometry, imaging or laboratorial data), thus relying exclusively on the subjective assessment of the five senses for confirmation or exclusion of possible patterns. Among these examinations, pulse palpation is probably the most famous and intriguing one, since antiquity until present days<sup>[22]</sup>.

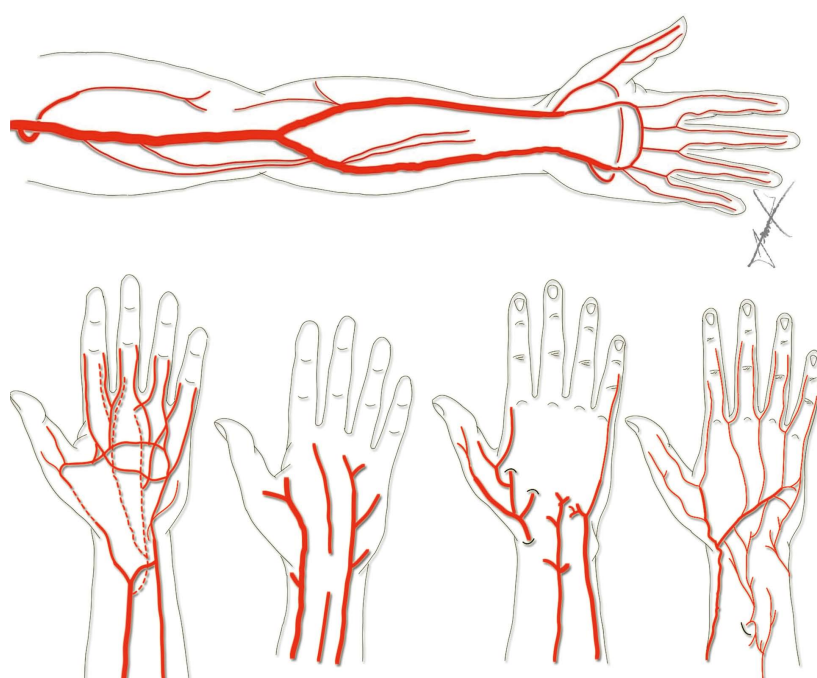
Fundamental attributes of the arterial pulse such as frequency, rhythm, wideness, and depth are shared between Chinese and evidence-based medical practices. Descriptions of abnormal pulses as palpated at either the radial or carotid artery are established for clinical diagnosis of patients with cardiovascular diseases (CDV)<sup>[23]</sup>. Chinese medicine practitioners also make use of subjective attributes to describe their feeling of the pulse – the so-called *pulse image*<sup>[22]</sup>. Figure 1 exhibits the network of all 27 pathological pulse images from descriptions arranged by attribute<sup>[22]</sup> as generated by Cytoscape 3.0.0<sup>[24]</sup>. It can be observed that there are pulse images described by

exclusive attributes (e.g., “rapid” or “short” pulse), while other pulse images are described by shared attributes (e.g., “weak” or “fine” pulse). In particular, the “deep”, “fast”, “slippery”, “strong”, “thin” and “wiry” pulse images are frequently observed in patterns related to SAH (e.g., wiry pulse = 52%, thin pulse = 25.6%, deep pulse = 7%)<sup>[12]</sup>. Therefore, it is possible to assert that there is a relationship between the abnormal pulses and pulse images, although no evidence on this specific relationship in patients with SAH have been presented so far using quantitative pulse wave analysis.

In the last decades, pulse wave analysis using radial artery tonometry along with mathematical simulation and modeling has been used for the noninvasive assessment of both anatomic and functional status of arteries<sup>[25]</sup>. For instance, previous studies showed that patients with SAH may present increased pulse wave velocity and decreased radial artery compliance<sup>[25]</sup>, medium-sized arteries hypertrophic remodeling<sup>[26]</sup>, and impaired flow-mediated vasodilation characterized by smaller and slower radial artery vasodilation<sup>[27,28]</sup>. These adaptive characteristics

**Table 2** Summary description of studies on the neglected issues linking evidence-based and Chinese medicines

Ref.	Study characteristics	Main results	Main limitation
Anatomical variations of vessels			
Chen <i>et al</i> <sup>[43]</sup>	Cross-sectional observational study One hundred healthy subjects, of normal or abnormal pulses forty-six with pancreatitis, forty-two with duodenal bulb ulcer, twenty-two with appendicitis, and third-eight with acute appendicitis	Accuracy of 82% for classification using an auto-regressive model for analysis of wrist pulse signals (blood flow signal) and a support vector machine	Ultrasound-based blood flow measurements was subjected to manual positioning and operator experience Only one position was investigated (above the styloid process) Pattern differentiation was performed (in either group) and the results were not related to Chinese medicine theory
Huang <i>et al</i> <sup>[44]</sup>	Cross-sectional observational study Thirty normal subjects and thirty patients with palpitation	Higher spectral harmonic energy ratio in patients	Only 10 s were evaluated at each position Palpitation was only characterized by the evidence-based medicine and no correspondence to patterns was established Pattern differentiation was performed in either group and the results were not related to Chinese medicine theory Lack of relationship between spectral harmonic energy ratio and Chinese medicine theory for pulse palpitation
Hu <i>et al</i> <sup>[45]</sup>	Cross-sectional observational study Six normal subjects (all male)	No significant difference was observed on pulse waveform parameters obtained with single or array sensors Significant differences were observed among depths	Only one position was investigated (above the styloid process) Pattern differentiation was performed in either group and the results were not related to Chinese medicine theory

**Figure 2** Anatomical drawings on variations of the course of the radial artery. Top: Most frequent arterial pattern of the radial artery. Bottom: Examples of anatomical variations of the radial artery at the wrist.

may strongly impact on the perception of the pulse as palpated at the radial artery and are reflected in the pulse waveform signal as collected using arterial tonometry. For instance, a study showed that some spectral harmonics of the pressure pulse waveform (C0, C1, C3, C4 and C6) are higher in patients with SAH as compared to health controls<sup>[29]</sup>. However, a more recent study<sup>[30]</sup> failed to found a relationship between the traditional method of ‘simultaneous pressing’ for wrist pulse palpation and the spectral harmonics assigned to the respective internal organs.

### Herbal therapy

In the context of therapeutics for SAH, it was recently

proposed to merge the ancient knowledge with the current one, yielding “the earlier the better for treating who and what are not yet ill”<sup>[31]</sup>. This proposal also reflects the epidemiologic interpretation of traditional Chinese medicine while it is in agreement with the natural history of patterns related to SAH.

The use of herbs, minerals, and animal parts to compose medicinal formulas is acknowledged as the oldest therapeutic method in Chinese medicine. Considerable advances were recently achieved in the field of antihypertensive drugs, with several drug classes available for optimization of blood pressure control<sup>[3]</sup>. However, limited efficacy for reducing blood pressure levels and side ef-

fects are among the factors that lead researchers to study other therapeutic resources, including natural compounds used in traditional medicine recipes. A large number of information about cardioprotective food is currently available and the United States Food and Drugs Administration approved and recommended some of them, even though studies are not definitive about them.

More specifically related to Chinese medicine, a recent systematic review summarized evidences in favor of Chinese herbal therapy for patients with patterns related to SAH<sup>[32]</sup>. There are formulas that have been used widely in clinical practice for treatment of hypertension such as the *Banxia Baishu Tianma Tang* (Decoction of Pinellia ternate, Atractylodes and Gastrodia elata), *Da Chaihu Tang* (Major Bupleurum Decoction), *Liu Wei Dihuang Wan* (Pill of Rehmannia), and *Banxia Baishu Tianma Tang* (Decoction of Pinellia ternate, Atractylodes macrocephala, and Gastrodia elata). The general effects observed in previous studies include the reduction of blood pressure variability, inhibition of the activity of sympathetic nerve, blocking of the renin-angiotensin system, improvement of endothelial function and insulin resistance, and prevention of TOD<sup>[32]</sup>. Altogether, it is possible to assert that ancient Chinese medicine practitioners were aware of the potential benefits of herbs on the cardiovascular system. Despite these whole-body effects, there are still some challenges for a large-scale usage of herbal therapy for Chinese medicine patterns related to SAH including the quality control of compounds, interaction among formula's compounds, and dose-response effects.

## NEGLECTED ISSUES

In this section, the anatomical variations of vessels and comparative physiology are discussed. These issues are considered neglected because previous researches on integrative medicine ignored these aspects as related to the studies' main outcomes. Thus, these issues must be considered in future studies as factors for analysis and not as issues that could be assumed negligible. Table 2 presents summary information about the studies cited in this section.

### Anatomical variation of vessels

The radial artery is classically described at the wrist as passing deep to the tendons of the anatomical snuff-box (Figure 2, top). However, variations in the arterial pattern—i.e., number and/or course of the arteries—of the upper limb have been observed frequently either in routine dissections or in clinical practice<sup>[33]</sup> and are of both clinical and surgical significances<sup>[34-39]</sup>. Variations in the origin and proximal course of this artery are the most common anomalies found in the forearm (Figure 2). For instance, a study with 150 routine dissections of the brachio-antebrachial arterial axis from adults cadavers and 10 from full-term fetuses found that 7 cases showed high origin of the radial artery, and were divided into 2 groups where one had the presence of a median artery (3

cases) and the other had the absence of the artery (4 cases)<sup>[40]</sup>. Moreover, radial artery tortuosity, hypoplasia, and stenosis were observed in patients undergoing transradial coronary intervention<sup>[41]</sup>.

Chinese medicine literature states that the wrist pulse is generally felt above the styloid process of the radius and nearby proximal-distal regions in the arterial course, and that it is possible not to feel the pulse at these locations; in this case, one can feel the pulse at the external aspect of the wrist—and most importantly, it is not a sign of disease<sup>[42]</sup>. Thus, ancient Chinese medicine scholars were aware of the existence of anatomical variations of arteries and on the distinction between pulse images resulting from normal variations and morbid patterns.

Studies have been focusing on the modernization of Chinese medicine by incorporating devices (i.e., pressure sensors) and automated methods (i.e., software tools) to acquire pressure data from the radial artery<sup>[43-45]</sup>. However, it is intriguing that in spite of the above-cited traditional and current knowledges, none of these studies considered the anatomical variation as a confounding factor for either qualitative or quantitative pulse image analysis. Patients with hypertension are at an increased risk of presenting radial artery tortuosity<sup>[46]</sup>. Because the geometrical characteristics of the radial artery determine the transmission of the pressure pulse waveform along the vessel<sup>[26]</sup>, it is expected that patients with SAH present pulse image characteristics due to arterial tortuosity, vascular remodeling, or both. Therefore, the anatomical variation of the radial artery cannot be neglected in future studies on pulse image analysis since it may help explain the qualitative or quantitative observed pulse image.

### Comparative physiology

Recognized as the Father of western Medicine, Hippocrates (460-375 BC) and Huangdi (2695-2589 BC), reference inside the oldest known treatise of medicine in existence (the *Huangdi Neijing*) had in common in their discussions the use of acupuncture for treatment of various diseases, including coronary artery disease<sup>[47]</sup>. Hippocrates advocated the theory of four humors—earth, air, fire and water—when trying to explain the pathogenesis of a disease, analogous to the five-phase theory of Huangdi—wood, fire, earth, metal and water. This example of comparative reasoning can be extended to all major fields of medical knowledge in Chinese and evidence-based medicines: anatomy, physiology, semiology, pathophysiology, and therapy. It is acknowledged that there are important conceptual differences between these medical practices as related to the body structures<sup>[48]</sup>, but strong similarities are empirically present at the functional level. As related to the circulatory system, Chinese medical theory also recognize its role on several functions such as the whole-body integration for distribution of substances, regulation of body temperature, and the relationship between circulation and life support<sup>[48]</sup>.

Researchers are investigating Chinese medicine searching for anatomical and/or physiological explana-

tions for the phenomena related to the safety-efficacy of interventions in the patients with SAH and other CVD<sup>[10]</sup>. However, it is apparent that no comparative analysis have been systematically performed between Chinese and evidence-based medical theories. More specifically, it is not a matter of translation of terms from Chinese to English, but to properly transpose the interpretation of Chinese medicine knowledge to its counterpart in evidence-based medicine. For instance, such comparative reasoning may help explain: (1) the strong association observed between descriptions of TOD and patterns in patients with SAH; and (2) the similarities and dissimilarities between abnormal pulses, quantitative pulse waveform analysis, and qualitative pulse images. Therefore, it is recommended to not neglect the study of a comparative physiology between these two medical practices since it may improve our understanding on the natural history of SAH and the potential benefits of an integrated approach to patients undergoing cardiac rehabilitation programs.

## DISCUSSION

Complementary and alternative medicine (CAM) are increasingly available and used for health care. A study<sup>[49]</sup> that analyzed data on CAM use among patients with CVD found that 36% of patients with CVD had used CAM in the previous 12 mo and 10% respondents used CAM specifically for their cardiovascular conditions—among which 5% for hypertension, 2% for coronary disease, and 3% for vascular insufficiency. The same study showed that cardiac patients use mind-body therapies including deep-breathing exercises, group support, hypnosis, meditation, relaxation, *taijiquan*, *yoga*, and *shiatsu*, among others<sup>[49]</sup>. Acupuncture, herbal Chinese medicine, moxibustion, cupping, Chinese massage, *qigong* and *taijiquan*, and dietary therapy<sup>[50]</sup>, when associated to antihypertensive medication significantly reduced systolic blood pressure (-8 mmHg) and diastolic blood pressure (-4 mmHg) with no heterogeneity detected, although given the poor methodological quality and small sample sizes of most acupuncture trials, the notion that acupuncture may lower high blood pressure remains inconclusive<sup>[51]</sup>.

In summary, the asserted issues highlighted in this paper stimulate the increasing use of Chinese medicine for health care and the continuity of research on integrative medicine in the cardiovascular field. Conversely, the neglected issues poses additional challenges that must not be overlooked in future research on this topic so that the integration of both traditional and current knowledge may be of benefit to the population with CVD.

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