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L'amélioration du tonus vagal cardiaque : un levier d'avenir en oncologie ?

Enhancing cardiac vagal tone: a promising therapeutic lever for the future of oncology?

Sous la direction de : Fabrice JOULIA, PhD et Géraud GOURJON, PhD

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VAE - Partie 2 : Analyse du travail, des méthodes et des résultats scientifiques d'une ou plusieurs recherches déjà effectuées et Partie 3 : Productions scientifiques

Résumé

Titre : L'amélioration du tonus vagal cardiaque : un levier d'avenir en oncologie ?

Ce document constitue les Parties 2 et 3 de mon dossier de candidature à la Validation des Acquis de l'Expérience (VAE) pour l'obtention du doctorat de l'Université de Toulon. Destinées à être rendues publiques, ces sections présentent d'une part une analyse détaillée de mes travaux, de leurs fondements méthodologiques et de leurs résultats (Partie 2), et d'autre part, l'ensemble de mes productions scientifiques (Partie 3).

Ce manuscrit porte sur l'avancement des connaissances en physiologie du système nerveux autonome (SNA), plus particulièrement du tonus vagal cardiaque, et explore son rôle potentiel dans le cancer. Ces recherches ont été conduites en tant que chercheur associé au sein des structures suivantes : Laboratoire J-AP2S (Jeunesse – Activité Physique et Sportive – Santé) (Université de Toulon), service d'Onco-hématologie (Centre Hospitalier d'Avignon), et Pôle de Recherche Ostéopathique et Scientifique (Institut de Formation en Ostéopathie du Grand Avignon). Elles sont également menées en tant que Représentant scientifique de l'association Cancer et Métabolisme de Nîmes.

Le tonus vagal cardiaque (TVC) a émergé comme un levier pronostique et thérapeutique prometteur en oncologie, mais les mécanismes physiopathologiques sous-jacents à son rôle dans le cancer restent insuffisamment compris. Ce manuscrit présente une série d'études interconnectées visant à construire un cadre cohérent pour le domaine de l'onco-rythmologie.

Nous établissons d'abord un protocole méthodologique rigoureux pour la mesure du TVC chez les patients atteints de cancer, en identifiant sept facteurs confondants clés qui doivent être contrôlés afin d'assurer une évaluation fiable de la variabilité de la fréquence cardiaque (VFC). Nous montrons ensuite que les tests d'écoute ostéopathique, souvent supposés moduler le tonus autonome, ne produisent pas de modifications mesurables de la VFC, clarifiant ainsi ce qui constitue, ou ne constitue pas, un stimulus vagal valide.

Pour mieux comprendre le contexte dans lequel la modulation vagale est pertinente, nous proposons un paradigme novateur de carcinogenèse « la Mitochondrial-Stem Cell Connection » (MSCC) qui intègre la dysfonction métabolique et la biologie des cellules souches cancéreuses pour expliquer l'initiation tumorale, la progression et la résistance aux traitements, tout en fournissant les bases physiopathologiques permettant de comprendre pourquoi le microenvironnement tumoral supprime systématiquement l'activité vagale efférente. Nous examinons ensuite la plongée en apnée comme un stimulus vagal exceptionnellement puissant

et entraînable, en mettant en évidence ses mécanismes au niveau du tronc cérébral et son potentiel pour améliorer durablement le TVC. Nous synthétisons également les données sur le rôle ambivalent du nerf vague dans les cancers à innervation vagale directe, en distinguant les effets suppressifs d'une stimulation afférente excessive du rôle potentiellement protecteur de l'amélioration efférente. Enfin, nous documentons que les traitements oncologiques standards induisent systématiquement une hyperglycémie (un facteur qui alimente directement le métabolisme tumoral) renforçant ainsi la logique d'une prise en charge conjointe métabolique et autonome en oncologie.

Ensemble, ces travaux convergent vers une hypothèse thérapeutique novatrice : restaurer le TVC par un exercice structuré en apnée, combiné à une gestion métabolique, pourrait représenter une stratégie complémentaire efficace et non invasive en oncologie.

SUMMARY

Title: Enhancing cardiac vagal tone: a promising therapeutic lever for the future of oncology?

This document constitutes Parts 2 and 3 of my application file for the Validation of Acquired Experience (VAE) for the award of a doctoral degree from the University of Toulon. Intended to be made public, these sections present, on the one hand, a detailed analysis of my research, its methodological foundations, and the results obtained (Part 2), and on the other hand, a compilation of my scientific outputs (Part 3).

This manuscript focuses on advancing knowledge in the physiology of the autonomic nervous system (ANS), particularly the cardiac vagal tone, and explores its potential role in cancer. These research studies were conducted as an associated researcher within the following institutions: J-AP2S Laboratory (Youth – Physical Activity and Sports – Health) (University of Toulon), the Onco-Hematology Department (Avignon Hospital Center), and the Osteopathic and Scientific Research Center (Institute of Osteopathic Training of Greater Avignon). They are also conducted in the capacity of Scientific Representative for the Cancer and Metabolism Association of Nîmes.

Cardiac vagal tone (CVT) has emerged as a promising prognostic and therapeutic lever in oncology, yet the pathophysiological mechanisms underlying its role in cancer remain insufficiently understood. This manuscript presents a series of interconnected research studies aimed at building a coherent framework for the field of onco-rhythmology.

We first establish a rigorous methodological protocol for measuring CVT in cancer patients, identifying seven key confounding factors that must be controlled to ensure reliable heart rate variability (HRV) assessment. We then demonstrate that osteopathic listening tests, often assumed to modulate autonomic tone, do not produce measurable changes in HRV – clarifying what does and does not constitute a valid vagal stimulus.

To better understand the context in which vagal modulation matters, we propose a novel paradigm of carcinogenesis – the Mitochondrial-Stem Cell Connection (MSCC) – which integrates metabolic dysfunction and cancer stem cell biology to explain tumor initiation, progression, and treatment resistance, and which provides the pathophysiological foundation for understanding why the tumor microenvironment systematically suppresses vagal efferent activity.

Building on this, we examine breath-hold diving as an exceptionally potent and trainable vagal stimulus, elucidating its brainstem mechanisms and its potential for sustained CVT improvement. We then synthesize evidence on the ambivalent role of the vagus nerve in vagally-innervated cancers, distinguishing the suppressive effects of afferent overstimulation from the potentially protective role of efferent enhancement. Finally, we document that standard oncological treatments consistently induce hyperglycemia – a factor that directly feeds tumor metabolism – reinforcing the rationale for metabolic and autonomic co-management in cancer care.

Together, these studies converge toward a novel therapeutic hypothesis: that restoring CVT through structured breath-hold exercise, combined with metabolic management, may represent an effective and non-invasive complementary strategy in oncology.

VAE - Partie 2 : Analyse du travail, des méthodes et des résultats scientifiques de plusieurs recherches déjà effectuées

Et

Partie 3 : Productions scientifiques

Acknowledgments

I would first like to thank the University of Toulon, which gave me the opportunity to undertake this VAE project, a project that, I hope, will allow me to fulfill a childhood dream.

This project would not have come to fruition without the unwavering support of three key individuals who played a major role in my journey and trusted me. First, thanks to Fabrice, my thesis supervisor, for his unwavering support, his humility, remarkable positivity, and passion, which, after such an impressive career, continue to shine and inspire everyone around him. I thank you for your constant kindness towards me and for agreeing to accompany me on this unconventional path. Then, also thanks to Géraud, my thesis co-supervisor, for his constant support over the years. I thank you because you were the first to initiate me, and we probably would not have, either you or I, bet on such a path together today. Your rigor, which has earned you such a reputation, has been immensely helpful, and I owe a great deal of this journey to you.
I am very grateful to both of you, and I am aware that I owe you a great deal. It has been a privilege to work with you, and I hope this collaboration will continue for many years to come.

I would also like to express my deep gratitude to Pascale Duché, the director of my laboratory, for placing her trust in me, without which this project would not have been possible.

I would like to sincerely thank all the co-authors with whom I have had the privilege to work throughout my research career. Your expertise, guidance, and collaboration have been invaluable in shaping the scientific work presented in this thesis. I am particularly grateful to: Makis William, Baghli Ilyes, Grant William. B, Sabatier Jean-Marc, Dutschmann Mathias, Epercieux Vincent, Grinand Marilyne, Cheggour Saïda, Taieb Jérôme, Gillet Flora, Gault Mathilde, Dussault Vincent, Quincampois Nicolas, Chaix Adélaïde, Seyfried Thomas N, Slama Borhane, Guieu Régis. Each of you has enriched my scientific journey, and your collaboration has been essential to the work presented here. I am deeply grateful for your support, inspiration, and dedication.

Finally, a special thank you to my Family for their indescribable and invaluable support throughout these long years. You have shown great selflessness and have made so many sacrifices for me, and I will be grateful to you for the rest of my life.

Thank you to research for bringing us together and for making the realization of this project possible.

Preface

This document presents the Part 2 and the Part 3 of my application for the Validation of Acquired Experience (VAE) for the doctoral degree from the University of Toulon. As per the VAE guidelines, Part 2 and Part 3 are publicly available, while Part 1 remains confidential.

Part 2 offers a comprehensive analysis of the research work, methodologies, and scientific outcomes I have contributed to throughout my career. It primarily focuses on the advancements in understanding the ANS, particularly the vagus nerve, and its potential involvement in cancer progression. This research was conducted at the Onco-Hematology Department of the Avignon Hospital Center, in collaboration with the Osteopathic and Scientific Research Pole, alongside my roles with the Cancer and Metabolism Association and the J-AP2S Laboratory (Youth – Physical Activity and Health).

Part 3, titled “Scientific Productions”, compiles a selection of my peer-reviewed publications, conference contributions, and technical reports that mark key milestones in my academic journey.

This document (Parts 2 and 3) complements Part 1 of the VAE application, which remains confidential. Part 1 is divided into two main sections:

- Part 1A details my career development as a researcher, outlining the competencies I have acquired and the coherence of my research activities over the years.

- Part 1B describes three major research projects, each with a clear presentation of the project’s context, goals, methodology, the work undertaken, and the knowledge and skills mobilized during the course of the project.

In its entirety, this VAE application (Parts 1, 2, and 3) provides a thorough overview of my research career and achievements, with Parts 2 and 3 being the publicly accessible components.

Table of contents

Summary 3
Acknowledgments 6
Preface 8
Table of contents 9
List of figures 13
List of tables 15
Acronyms and abbreviations 16
1. Chapter 1: Introduction and Research Objectives 18
1.1 Context: The Autonomic Nervous System and Cancer 18
1.2 Research Objectives 19
1.3 Structure of this dissertation 19
2. Chapter 2: How to properly evaluate the cardiac vagal tone in oncology? 21
2.1. Introduction 21
2.2. Study selection 23
2.2.1 Data source 23
2.2.2 Data collection and analysis 24
2.2.3 Choice of HRV metrics 24
2.3. Main HRV measurements 24
2.3.1 Time-domain variables 25
2.3.2 Frequency-domain variables 26
2.3.3 Metrics specific to cardiac vagal tone and HRV 27
2.4. Reference data in healthy and cancer patients 29
2.5. External factors' influence 33
2.6. Collecting data 38
2.6.1 Recording duration 38
2.6.2 Measurement tools 39
2.6.3 Analysis software 39
2.6.4 Artifact corrections 39
2.7. Suggested protocol to evaluate cardiac vagal tone in oncology 41
2.8. Conclusion 42
3. Chapter 3: Can osteopathic tests influence heart rate and heart rate variability? 44
3.1 Introduction 44

3.2 Methods 45
3.2.1 Population 46
3.2.2 Randomization 47
3.2.3 Protocol 48
3.2.4 Heart rate and heart rate variability measures 50
3.2.5 Statistical analysis 51
3.3 Results 51
3.3.1 Population 51
3.3.2 Main results 51
3.4 Discussion 54
3.4.1 Interpretation 54
3.4.2 Limits 56
3.4.3 Generalizability 56
3.5 Conclusion 57
4. Chapter 4: Time to reconsider the paradigm of carcinogenesis? 58
4.1. Introduction 58
4.2. The Somatic Mutation Model Alone May Not Explain Tumorigenesis 59
4.3. Role of Mitochondria in Tumorigenesis 60
4.4. Nuclear Genetic Mutation Versus Mitochondrial Alteration in Tumorigenesis: Experimental Studies 62
4.5. Cancer Stem Cells (CSCs) Are Induced by Mitochondrial Damage in Stem Cells: The Origin of Tumorigenesis 65
4.6. The Metabolism of Cancer Cells Compensates for OxPhos Insufficiency 67
4.7. CSCs and Macrophages: The Origin of Metastases 70
4.8. The Tumor Microenvironment of CSCs: A Necessary Consequence of Mitochondrial Impairment 71
4.8.1. Pressure and Deformation of Tissues 71
4.8.2. pH 71
4.8.3. Hypoxia 72
4.8.4. Entropy 72
4.8.5. Temperature 73
4.8.6. Stroma 73
4.8.7. Bioelectricity and Cancer 73
4.8.8. Cytoplasmic Water 73

4.9. The CSCs (and Their Mitochondria), an Explanation of the Current Treatments and Relapses 74
4.10. Key Points of the MSCC 76
4.11. Conclusions 78
5. Chapter 5: Physiological basis of cardiac vagal tone in breath-hold diving 80
5.1 Introduction 81
5.2 The central mediation of respiratory Heart Rate Variability (respirHRV) 82
5.3 Control of cardiac vagal motor neurons during reflexes and volitional breath-hold 86
5.4 Converging multi-modal sensory and cardiac vagal motor pathways in the brainstem gate the diving bradycardia 88
5.5 Additional sensory mechanisms during short and prolonged breath-hold dives in animals and humans 91
5.5.1 Lung stretch receptor (Hering Breuer reflex) mediated modulation of the diving bradycardia 91
5.5.2 Arterial chemoreceptor evoked modulation of the diving bradycardia 93
5.6 Learning how to elicit a diving bradycardia 94
5.7 Evidence for health benefits linked with regular Breath-hold dive exercise 97
5.8 Therapeutic potential of breath-hold diving 98
6. Chapter 6: The forgotten role of the vagus nerve in cancer? 100
6.1 Introduction 101
6.2 Afferent tumor-CNS pathways 102
6.2.1 Spinal sensory neurons 102
6.2.2 Vagal Sensory Afferents: An Underexplored Pathway for Tumor-CNS Communication? 103
6.2.3 Inflammation, Cytokines, and Cancer Progression 104
6.2.4 Vagal Sensory Receptors Potentially Transmitting Tumor Microenvironment Information 104
6.3 Interplay Between the Vagus Nerve, Microbiome, and Renin-Angiotensin System (RAS) in tumors in vagal-innervated organs 109
6.4 Neuro-circulatory integration in Central Nervous System 113
6.5 Efferent Central Nervous System-Tumor pathways 115
6.5.1 Do sympathetic and parasympathetic efferents influence cancer? 115
6.5.2 Systemic inhibition of vagal efferent fibers in tumors in vagal-innervated organs? 118

6.5.3 Chronic cancer stress engages sympathetic and neuro-immuno-endocrine pathways, impacting various other physiological systems 121
6.6 Current Experimental Approaches: Limitations and Future Directions 124
6.7 Conclusions and perspectives 125
7. Chapter 7: Cancer treatment and glycemic outcomes: a systematic review and meta-analysis. 127
7.1 Introduction 128
7.2 Research design and methods 130
7.3 Results 133
7.4 Discussion 145
7.5 Conclusion 149
8. Chapter 8: Conclusions and future perspectives 150
8.1 Key strengths and limits 151
8.2 Conclusion on achievements and future perspectives 151
Chapter 9: References 153

List of figures

Figure 2.1: QRS complex and RR interval. ms, milliseconds; RR interval, interval between two R peaks. 25
Figure. 2.2 Differences between normal ECG (top) and ECG with artifacts (bottom). ECG, electrocardiogram. 40
Figure 3.1: Flow chart for the observational study. 48
Figure 3.2: Tests protocol for the different groups. 49
Figure 3.3: Histogram of the means of the different metrics before and after the protocol. 53
Figure 4.1. Dysfunctional mitochondria drive the alterations seen in the nuclear genome. 63
Figure 4.2. Nuclear genetic mutation versus mitochondrial dysfunction. 64
Figure 4.3. The OxPhos alteration in stem cells induces the Cancer Stem Cells. 67
Figure 4.4. The glycolysis and glutaminolysis pathways in cancer cells. 69
Figure 4.5. The tumor-scale microenvironment is shown on the left. In the enlarged window at the bottom right, the microenvironment is represented at the cellular level. 74
Figure 4.6. Synthesis of MSCC. 77
Figure 5.1. Simplified representation of excitatory and inhibitory synaptic neurons involved in the simultaneous generation of the respiratory motor pattern and respiratory sinus arrhythmia of the heart. 84
Figure 5.2. Indirect control of cardiac vagal tone via volitional breath-hold. 87
Figure 5.3. Schematic illustration of sensory inputs and central pathways that mediate the nasotrigeminal (diving) reflex. 89
Figure 5.4. Diminished drive from lung pulmonary stretch receptors is enhancing the diving bradycardia. 92
Figure 5.5. Chemoreceptors input facilitates the diving bradycardia. 93
Figure 5.6. NMDA-receptor plasticity associated with diving exercise. 96
Figure 6.1. Summary of Tumor-CNS Communication via Afferent Sensory Nerve Fibers in Vagal-Innervated Organs. 114
Figure 6.2. Systemic inhibition of vagal efferent fibers in tumors in vagal-innervated organs. 120
Figure 6.3. A comprehensive summary of efferent pathways involving the central nervous system and tumors. 122

Figure 7.1: Prisma Flow Diagram of Included Studies. 134
Figure 7.2: Effect of treatment on hyperglycemia across 28 studies using the Freeman–Tukey double–arcsine transformation and a random-effects model (DerSimonian–Laird) 143

List of tables

Table 2.1. Main HRV metrics and analysis domains useful in oncology. 28
Table 2.2. Observed data in healthy and cancer patients. 30
Table 2.3. Physical activity's effect on HRV metrics in healthy and cancer patients. 34
Table 2.4. Chemotherapy's effect on HRV metrics in cancer patients. 35
Table 2.5. External factors' effect on HRV metrics in healthy patients. 36
Table 3.1: Demographic information in osteopathic test group, light pressure group and control group. 47
Table 5.1. Long-term (24 h) variation of cardiac vagal tone in divers. 97
Table 6.1. Potential Sensory Stimuli from the Tumor Microenvironment Transmitted via the Vagus Nerve. 108
Table 6.2. Status of the renin-angiotensin system and the microbiome in tumors in vagal-innervated organs. 112
Table 7.1: Risk of mortality of major cancer related to hyperglycemia. 129
Table 7.2. Characteristics of included studies in systematic review. 136
Table 7.3 Summary of the subgroup meta-analysis. 145

Acronyms and abbreviations

- Accelerated Capacity (AC)
- Acetylcholine (ACh)
- Adenosine triphosphate (ATP)
- Angiotensin II (Ang II)
- Angiotensin-converting enzyme (ACE)
- Angiotensin receptors 1 and 2 (AT1R and AT2R)
- Autonomic nervous system (ANS)
- AutoRegressive (AR)
- Beats per minute (bpm)
- Breath-hold dive (BH-D)
- Cancer stem cells (CSCs)
- Cardiac vagal motoneurons (CVMNs)
- Cardiac vagal tone (CVT)
- C-reactive protein (CRP)
- Central nervous system (CNS)
- Confidence Intervals (CIs)
- Control group (CG)
- Corticotropin-releasing hormone (CRH)
- Deceleration Capacity (DC)
- Dorsal motor nucleus of the vagus (DMNV)
- Dorsal root ganglia (DRG)
- Electron transport chain (ETC)
- Electrocardiogram (ECG)
- Electroencephalography (EEG)
- Ethmoidal nerve (EN5)
- Fast Fourier transform (FFT)
- Functional Magnetic Resonance Imaging (fMRI)
- Glucose Transporter 3 (GLUT3)
- Glucokinase (GK)
- Glucose–Ketone Index (GKI)
- G protein-coupled receptor (GPCR)
- Growth hormone (GH)
- Heart rate (HR)
- Heart Rate Variability (HRV)
- High Frequency (HF)
- Hertz (Hz)
- HIF-1α (hypoxia-inducible factor 1α)
- Hypothalamic-pituitary-adrenal axis (HPA)
- Insulin-like Growth Factor one (IGF-1)
- Interleukin 1β (IL-1β)
- Ketogenic diet (KD)
- Kölliker-Fuse nucleus (KF)
- Low Frequency (LF)
- Magnocellular neurons (MCNs)
- Mitochondrial DNA (mtDNA)
- Mitochondrial-stem cell connection (MSCC)
- Mitochondrial substrate-level phosphorylation (mSLP)

- Neutrophil-to-lymphocyte ratio (NLR)
- N-Methyl-D-Aspartate receptors (NMDA-R)
- Nerve growth factors (NGFs)
- Nucleus ambiguus (nA)
- Nucleus tractus solitarii (NTS)
- Oxygen consumption rate (OCR)
- Osteopathic manipulative treatment (OMT)
- Osteopathic test group (OTG)
- Oxidative phosphorylation (OxPhos)
- ParaVentricular Nucleus of hypothalamus (PVN)
- Platelet-to-lymphocyte ratio (PLR)
- Pontine respiratory group (PRG)
- Pre-Bötzinger complex (pre-BötC)
- Premature ventricular contractions (PVC)
- Pyruvate kinase muscle isozyme (PKM)
- Randomized controlled trial (RCT)
- Renin-angiotensin system (RAS)
- Respiratory Heart Rate Variability (respirHRV)
- Respiratory Sinus Arrhythmia (RSA)
- Retrograde (RTG)
- Rostral ventrolateral medulla (RVLM)
- Short-chain fatty acid (SCFA)
- SDNN (standard deviation of all NN intervals)
- Soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1)
- Spinal trigeminal nucleus (Sp5C)
- Sympathetic nervous system (SNS)
- Systemic inflammatory index (SII)
- Tissue organization field theory of cancer (TOFT)
- Toll-like receptor 4 (TLR4)
- Tumor-associated macrophages (TAMs)
- Tumor microenvironment (TME)
- Tumor necrosis factors (TNF-α)
- Transient receptor potential ankyrin A1 (TRPA1)
- Transient receptor potential melastatin 8 (TRPM8)
- Transient receptor potential vanilloid type (TRPV)
- Very Low Frequency (VLF)
- Ventral respiratory column (VRC)
- Vasopressin (VP)
- 5-hydroxytryptamine (5-HT)

1. Chapter 1: Introduction and Research Objectives

The major part of this Chapter 1, and in particular Section 1.2 "Research Objectives" and Section 1.3 "structure of this dissertation," has been specifically developed in the context of this VAE application.

Section 1.1 "Context: The Autonomic Nervous System and Cancer" builds upon the multidisciplinary research I have conducted over the last five years in clinical physiology, fundamental physiology and physiopathology, oncology, and human performance. These investigations led to several peer-reviewed publications and the coordination of experimental and clinical studies. Full references and acknowledgements regarding the contribution of collaborators and co-authors are provided in subsequent chapters of this dissertation.

1.1 Context: The Autonomic Nervous System and Cancer

The autonomic nervous system (ANS), and in particular the vagus nerve, plays a crucial role in regulating homeostasis. Since the 1950s, growing attention has been paid to the physiological modulation of the vagus nerve and its implications for various chronic diseases. Over the past two decades, a body of evidence has emerged regarding the potential protective role of high cardiac vagal tone (CVT) in cancer prognosis, mainly through anti-inflammatory, antioxidative, and anti-proliferative mechanisms[1]. However, the pathophysiological mechanisms underlying these associations remain insufficiently understood, and many questions are yet to be resolved. My research explores the modulation of CVT as a lever to influence the tumor environment and patient outcomes in cancer. The investigations have been conducted in collaboration with several academic and clinical institutions, including the University of Toulon (UFR STAPS), the Clinical Research Department of the Avignon Hospital Center, and the Institut de Formation en Ostéopathie du Grand Avignon. This work seeks to better define the role of the vagus nerve in tumor biology and opens the path to an emerging interdisciplinary field: onco-rhythmology. The chapters that follow were not designed as independent studies, but as successive steps in a single investigative arc. Before vagal modulation can be proposed as a therapeutic strategy in oncology, several foundational questions must be answered: How should CVT be reliably measured in cancer patients? What interventions genuinely modulate it, and which do not? Why does the tumor environment systematically suppress vagal efferent activity? What physiological discipline is most capable of reversing this suppression? And what systemic

consequences – notably on glucose metabolism – must be addressed alongside vagal tone in clinical practice? Each chapter addresses one of these questions, and each answer informs the next.

1.2 Research Objectives

The central objective of this research is to assess and promote CVT as a physiological lever with potential therapeutic implications in oncology.

To achieve this, the following specific objectives have been identified:

- To identify and validate reliable measurement protocols of CVT in cancer patients;
- To explore the physiological and experimental conditions that modulate CVT in healthy individuals and in cancer patients (e.g., breath-hold diving, osteopathic stimulation, ventilatory techniques);
- To investigate the theoretical, mechanistic and metabolic basis of the vagus nerve's role in carcinogenesis and tumor progression;
- To highlight the dual and context-dependent role of the vagus nerve across different cancers, particularly those located in vagally innervated organs;
- To provide an integrative framework for using vagal modulation as part of future therapeutic strategies in cancer care.

1.3 Structure of this dissertation

Chapter 2 presents a protocol developed from the results of a randomized controlled trial conducted in 2021. This chapter discusses the limitations and lessons learned from the study.

Chapter 3 explores the effects of osteopathic interventions on CVT through an observational study conducted on healthy students.

Chapter 4 proposes a novel conceptual framework on the origin of cancer, combining insights from mitochondrial dysfunction, stem cell theory, and vagal tone modulation.

Chapter 5 analyzes the effects of breath-hold diving on vagal modulation and discusses the theoretical updates required in light of physiological observations.

Chapter 6 challenges the classical binary model of sympathetic versus parasympathetic systems and investigates the ambiguous role of the vagus nerve in certain cancers.

Chapter 7 evaluates the effect of standard oncology treatments on blood glucose levels.

Chapter 8 concludes this dissertation by synthesizing key findings, limitations, and future research perspectives in the field of onco-rhythmology.

2. Chapter 2: How to properly evaluate the cardiac vagal tone in oncology?

This Chapter is essentially drawn from:

Martinez P, Grinand M, Cheggour S, Taieb J, Gourjon G. How to properly evaluate cardiac vagal tone in oncology studies: a state-of-the-art review. J Natl Cancer Cent. 2024 Feb 13;4(1):36-46. doi: 10.1016/j.jncc.2024.02.002.

General abstract and Key Points of the Article:

This article provides a synthesis of the limitations identified in the literature and in our randomized controlled trial (RCT) conducted in 2021. It was written to share the gaps we encountered and to allow other researchers to avoid facing the same issues.

The article summarizes:

- All available data on heart vagal tone measurements in oncology,
- The various factors that can influence HRV before measurement,
- How to avoid and treat artifacts so that the data is usable,
- A protocol is provided to properly assess heart vagal tone.

This article allowed me, as part of my thesis, to define all the reference measures in patients and identify the various factors that can affect data quality.

2.1. Introduction

Homeostasis maintains the body in a healthy condition by regulating its constants and various functions. Among its main factors, the vagus nerve acts as a guardian [1] and works closely with the endocrine and immune systems[2,3]. Vagal tone is also related to the ANS. The latter can be divided into the parasympathetic nervous system (PSNS) and the sympathetic nervous system (SNS). The ortho-parasympathetic balance is controlled by the vagus nerve. SNS activity increases as vagal tone decreases, and conversely. Several publications described the physiology of ANS, SNS/PSNS regulation, and HRV clinical use[4-6].

The vagus nerve regulates metabolic homeostasis by controlling the heart rate (HR) [7], but also the interval between two heartbeats. The variability of this interval over time is called Heart Rate Variability (HRV)[6]. HRV provides an indirect measure of vagal tone, because it is primarily under the influence of cardiac vagal control. [8,9] Laborde et al. [10] and Shaffer et al. [11] reviewed HRV and its control by CVT.

HRV analysis provides an assessment of ANS conditions and consequently global cardiac health[12]. In diseases, especially systemic ones such as cancer, and during treatments that affect the whole body, like chemotherapy, the vagus nerve activity is deregulated[13]. This has an impact on both the ANS and the HRV. This deteriorates homeostasis and further increases systemic problems.

The clinical interest of HRV was only recognized in 1963 by Hon and Lee [14] who noted that acute alterations in HRV were a marker of fetal distress and predicted fetal hypoxia. It is thus possible to diagnose a physiological imbalance by evaluating the action of the cardiac vagal nerve/tone via HRV. Since then, many studies have focused on using HRV to predict cardiac health and mortality [15], especially in oncology, because cancer patients have low cardiac vagal activity [16,17]. Lin et al. [18] observed that HRV in patients with metastatic cancer was lower than in patients without metastasis, and an increased HRV correlates with a better vital prognosis of cancer patients [13,17,19-25], while a high resting heart rate has been shown to be predictive of cancer mortality [21,26]. In addition, several studies show that vagotomy accelerates tumor growth [27,28]. Globally, vagus nerve-cancer interactions have been highlighted [29] and proper vagus tone reduces the influence of other personal factors on prognosis, such as age or sex [30,31].

Thus, stimulation of the vagus nerve has therapeutic potential in oncology[32], like anti-metastatic effects [33]. As the vagus nerve regulates HRV, its stimulation would increase HRV and indirectly vital prognosis [17]. Indeed, the vagus nerve can inhibit oxidative stress, inflammation and excessive orthosympathetic activity [13,17]. Nevertheless, stimulation of the vagus must be adapted to the type of patient and the use of HRV must consider practical expectations of professionals: sensitivity to change, rapid feedback, easy to administer, low cost, noninvasive, reliable, etc.

Considering the interest of HRV measurement in oncology, some authors published reviews describing the benefits and the limitations of such metrics [16,17,23,24]. Nevertheless, the HRV assessment protocol has to be as suitable as possible for clinical practice and as unbiased as

possible in its endpoint to properly diagnose the CVT in cancer patients. Many HRV metrics exist, including rMSSD (square root of the mean of the sum of the squares of differences between adjacent Normal to Normal NN intervals) and SDNN (standard deviation of all NN intervals), which are the most used in oncology. Estimating and understanding these metrics is one of the main issues as well as the most complex.

References have been established in healthy patients and those with cardiovascular disorders [6], but they are used for patients in oncology as well [34,35]. However, in some diseases, HRV may be altered by various factors (duration and time of measurement, respiration, drugs, etc.), particularly in oncology where systemic alterations substantially increase artifacts, especially atrial ectopic beats [36]. Currently, an SDNN below the 50 milliseconds (ms) threshold in a healthy patient is considered pathological [37].

Our review aims to improve the CVT assessment in cancer patients. It presents the main HRV metrics currently used in oncology studies, their links with vagus nerve and cancer, their circadian fluctuations, as well as the influence of confounding factors and the choice of measurement duration. Finally, we talk about artifacts and software for HRV analysis to finally propose a specific protocol for an HRV measurement in patients with cancer.

2.2. Study selection

2.2.1 Data source

Electronic searches were conducted between January 2021 to July 2023 using MeSH and non-MeSH terms. We firstly investigated two databases, PubMed and ScienceDirect. These databases were supplemented by searching in publications' references (snowball procedure), and through google scholar and specific peer-reviewed journals, since few studies were not available on databases. No language or date restrictions were applied.

The included articles were clinical trials, randomized or not, observational studies, preliminary or pilot studies, narrative and systematic reviews, meta-analysis, and case reports. The following keywords were used: heart rate variability, HRV, CVT, vagal tone, vagus nerve, autonomic nerve system, sympathic nervous system, healthy patients, cancer, prognosis, and all metrics' names.

Studies were to focus on healthy and/or cancer patients and were to include HRV measures. No selection was done concerning treatments, types of cancer or cancer stages since information on terminal cancer patients is important for the prognosis role of HRV. However, studies on children or on cancer patients suffering from a concomitant disease (cardiac disease for example) were excluded. Lists of studies were imported to Microsoft Excel and duplicates were removed.

2.2.2 Data collection and analysis

Two investigators independently identified studies meeting inclusion criteria on the basis of titles then abstracts. One investigator extracted all data concerning HRV metrics, duration and time of measurement, software, tools (Electrocardiogram, Chest belt, etc.), breathing procedures, artifacts (Yes/No), chemotherapy or radiotherapy (Yes/No), types of cancer, and all confounding factors in HRV measurements. A second author verified extracted data. If data appeared in more than one study, we used the primary publication. A consensus between all authors was settled when differences of opinion arouse during data extraction. Assessment of studies' quality was not performed.

We pooled the data of a given metric if data were given for cancer patients and not only for healthy patients. For example, no data exists for Respiratory Sinus Arrhythmia (RSA), HRV triangular Index (HRVI) or Total power in cancer patients, so these metrics were excluded from analysis.

2.2.3 Choice of HRV metrics

Considering that HRV has only been used in oncology for a few years, HRV metrics were selected mainly on the basis of available data and their relevance to assess CVT. Consequently, data for some HRV metrics were excluded from our review, even if they had been used for patients with other diseases.

2.3. Main HRV measurements

A number of methods can be used to calculate variations in heart rate [38], basically classified in non-linear and linear methods. We focus on the latter one, which includes time-based and

frequency-based methods, because they provide metrics used in oncology to analyze the HR variation in the short term (around 5 minutes monitoring period) and/or long term (24 hours) [39]. Some authors suggested ultra-short term measurement periods of 60 seconds (s) [40] to 240s [41], but these periods do not appear to be appropriate in oncology as discussed later.

2.3.1 Time-domain variables

The time-domain analysis consists of monitoring heart rate data over a given period of time. In a continuous electrocardiogram (ECG) record, metrics are calculated from the interval between two R peaks (RR interval) of the QRS complex (Fig. 2.1). However, this interval may include ectopic beats, mainly considered as artifacts, which should be excluded from the analysis. The "cleaned" RR interval, without artifacts that bias results, is called Normal to Normal interval (NN interval), on which HRV parameters must be estimated. This time-method is better for short-term recordings analysis [42]. The metrics are expressed in original units (ms). This domain includes several metrics such as SDNN or rMSSD.

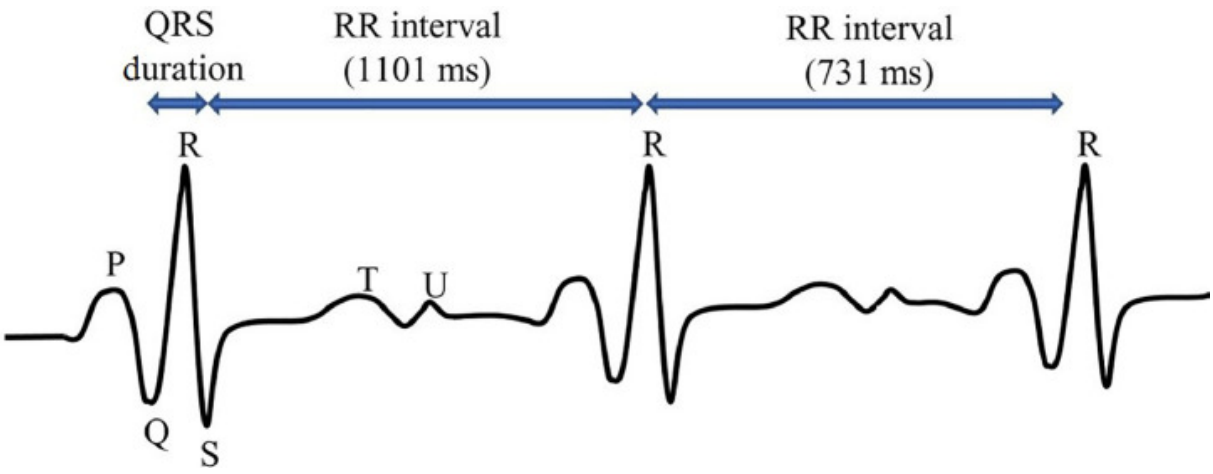


Figure 2.1 QRS complex and RR interval. ms, milliseconds; RR interval, interval between two R peaks.

SDNN. Standard deviation of NN intervals throughout the recording period. While considered as the gold standard of HRV, SDNN is not specific to the vagus nerve and does not reflect the CVT only. It reflects both cardiac vagal and sympathetic functions [10,43].

rMSSD. Square root of the mean of the sum of the squares of differences between adjacent NN intervals. It is known as a good estimate of PSNS activity and reflects the short-term variation of HR [10,44,45]. rMSSD doesn't seem to be significantly affected by breathing rate in several studies [46-48], even if Laborde et al. describe less clear results [49]. However, rMSSD seems to be mainly affected by a respiratory arrest [50]. To the contrary, SDNN appears to be more impacted by breathing stimulations [51]. Consequently, it seems to be suitable for CVT measurement, especially in oncology.

NN50 count/pNN50. NN50 corresponds to the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. It requires a 2 minute (min) period [11]. The pNN50 is the percentage of successive RR intervals that differ by more than 50 ms. The pNN50 reflects short term variations of the HRV and the CVT [10,45], especially the PSNS function [22,44]. NN50 is strongly correlated with rMSSD [52].

DC/AC capacities. Deceleration Capacity (DC) and Acceleration Capacity (AC) of HR are recent measurements that seem to be relevant in oncology. DC is a measure of cardiac parasympathetic modulation capturing the lengthening of the RR interval over 2 to 4 successive beats; the opposite for AC. DC is more robust to artifacts and noise [53], while AC describes SNS activity and is not a measure of CVT.

2.3.2 Frequency-domain variables

The frequency domain provides information on the spectral density as a function of frequency of Inter-Beat Interval. Thanks to a Fast Fourier transform (FFT), one gets a relative distribution of different frequencies of the HRV components (HRV Power Spectrum). This technique identifies three main peaks: the High and Low frequencies (HF and LF, respectively; Power in High Frequency range and Power in Low Frequency range) and the Very Low frequencies (VLF). These frequency metrics are given in Hertz (Hz). Note that some software display autoregressive (AR) spectrum in addition to FFT spectrum, like Kubios software, and can compute metrics from both estimation methods, leading to different metric's values.

LF. The Low Frequency band (0.04 to 0.15 Hz) mainly represents PSNS and SNS activity but not whole CVT [10], as well as baroreceptor activity in resting conditions [54]. Thus, the LF power

can be produced by PSNS, SNS, blood pressure regulation by baroceptors or by the baroreflex activity [11,55].

HF. The High Frequency band (0.15 to 0.4 Hz) indicates PSNS activity [54]. It is mainly due to HR variations during breathing (RSA). Consequently, Grossman et al. [56] consider that it does not completely represent the CVT. Some other authors says that HF reflects short-term variation of HRV (as rMSSD does) and is a response to CVT changes.

LF/HF ratio. While LF illustrates PSNS and SNS activity and HF only PSNS activity, the LF/HF ratio provides information about the relation between both systems. A low ratio could mean a PSNS dominance. Yet, some authors warn that only a part of LF is due to PSNS and as a consequence, the ratio would not describe the vagal balance [57-59].

VLF. This band represents long-term regulation mechanisms, thermoregulation and hormonal mechanisms [6,10]. The Very Low Frequency (0.0033 to 0.04 Hz) is strongly related to mortality[15] and health [58].

RSA. It corresponds to HR variability due to breathing (increased during inhalation and decreased during exhalation). This low physiological variation of HR can be observed in a 0.15 to 0.4 Hz band. RSA is highly correlated to HF when breathing rate is comprised between 9 to 24 cycles per minute [54,60]. Several authors consider that RSA is not a direct measurement of vagus nerve activity [11,56,61,62], but rather a partial measurement [56]. Even if RSA is correlated to vagal tone, Farmer et al. [63] show that a significant proportion of CVT arises independently of RSA. The RSA may reflect the respiratory component of CVT, which is generated by the respiratory centers acting on the cardioregulatory centers [64]. Consequently, it should not be used to assess the CVT. Moreover, no long-term changes in CVT have been studied with current methods of respiratory stimulation (coherent breathing, biofeedback, etc.) and no data for cancer patients are available.

2.3.3 Metrics specific to cardiac vagal tone and HRV

Some metrics are specific to CVT, while others provide broader information. Thus, each of them describes different characteristics of the HRV and CVT, like the rMSSD which focuses on short-term variation and corresponds to the activity of the PSNS.

Table 2.1 presents the main HRV metrics that can currently be useful in oncology. Especially because no data are available for cancer patients or because they do not describe vagal tone, other metrics in the Time domain, such as, NN50 count, HRVI (HRV triangular index), AC and in Frequency domain, such as Total power, LnHF (natural logarithm of HF), Very Low Frequency VLF, Ultra Low Frequency ULF, and RSA show currently a limited interest.

Table 2.1. Main HRV metrics and analysis domains useful in oncology

Domain/Metric	Vagal tone	Unit	SNS/PSNS	Cause and reflected activity
Time-domain				
SDNN	Both [10,43]	ms	Both	Global HRV, reflecting cardiac vagal and SNS functions. Short- and long-term variations.
rMSSD	Yes [6,10,22]	ms	Both but mainly PSNS	Short term variation.
pNN50	Yes [10,22]	%	Both but mainly PSNS	Short term variation.
DC	Yes [65]	ms	Both but mainly PSNS	Short term variation.
Frequency-domain				
HF	Yes [6,10], No [11]	*	Both but mainly PSNS	Heart variability induced by breathing.
LF	Both [10]	*	Both [10] or SNS [66].	Baroreceptors activity.
LF/HF Ratio	Both [10]	none	Both [10]	SNS-PSNS balance [11]

* HF and LF peak = Hz, HF and LF absolute power = ms², HF and LF relative power = normalized unit (n.u.)

DC: Deceleration Capacity of heart rate HF: High Frequency; HRV: Heart Rate Variability; Hz: Hertz; LF: Low Frequency; ms: milliseconds; PSNS: ParaSympathetic Nervous System; pNN50: NN intervals more than 50ms; rMSSD: square root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals; RSA: Respiratory Sinus Arrhythmia; SDNN: Standard Deviation of all NN intervals; SNS: Sympathetic Nervous System

In the Frequency-domain, most publications display data in Absolute (ms^2) or Normalized power (n.u.). Some software, such as Kubios, display frequencies in Peak (Hz), Relative (%), and Logarithmic transform (log) as well. To improve analysis, Laborde et al.[10] advise to analyze several parameters together (such as rMSSD for PSNS and SDNN for the SNS and PSNS), in addition to unrelated to CVT ones.

2.4. Reference data in healthy and cancer patients

To properly assess treatment effects on HRV metrics, norms on healthy and unhealthy patients have to be defined. Various diseases affect CVT. For example, in cancer patients, a significant imbalance of the ANS is observed, resulting in an SDNN generally under 20 ms and an rMSSD under 30 ms. Even if SDNN jointly decreases with rMSSD in most of studies, SDNN seems to remain a better predictor of survival.

It has to be noticed that HRV metrics fluctuate along the daytime and display maximal and minimal values at specific times of the day. For example, SDNN reaches maximal values around 6 AM instead of midday for rMSSD. While circadian rhythm could affect HRV parameters, the time of measurement is of great importance. All measurements among a study have to be carried out within a 4 hour (h) range of time, preferentially early in the morning while maximum values are reached for most of the parameters. Moreover, special attention must be paid to cancer patients because of a particularly altered circadian rhythm [67].

Table 2.2 shows values for short and long-term measurements in healthy people as well as observed data on patients with cancers. No prognostic or survival data are available for RSA and LF.

Table 2.2. Observed data in healthy and cancer patients

Metric	Daytime peak	Healthy + n[ref]		Cancer patients + n[ref]	
		Long-term	Short-term	Prognosis	Observed data
SDNN	6-8 AM68,69	141±39 ms (n[6] = 228; n[70] = 274) 146±37 ms (n[71] = 543)	50±16 ms (n[72] = 21.438)**	Poor prognosis for SDNN ≤ 7.6 ms, n[53] = 39; ≤ 10 ms, n[73] = 97; ≤ 20 ms, n[74,75] = 103; 272; ≤40 ms, n[43] = 47; ≤70 ms, n[22] = 131. Reference data used in HRV studies: 20ms, n[74-77] = 113;103;272;38.	All cancers 21.65±16.78 ms, n[78]=657; lung 17±14.6 ms, n[76]=133; prostate 31.24±30.27 ms n[76]=246; ovarian 11.1 ms (min=1.93; max=74.5), n[79]=202.
rMSSD	12 PM80	27±12 ms (n[6] = 228) 41±21 ms (n[71] = 543)	42±15 ms, (n[72] = 21.438)**	Not a survival prognostic factor.20,53,76,77 Significant correlation with PSA levels at 6 months.76	All cancers 23.79±20.48 ms, n[78] = 657; lung NSLC 19.1±21.1 ms and prostate 32.34±40.25 ms, n[76]=246; breast 19.8±8.5 ms (<18 months after surgery) and 15.0±6.0 ms (>18 months after surgery), n[81] = 30; leukemia 26±11 ms, n[82] = 36; ovarian cancer 11.5 ms (min = 1.70; max=84.8), n[79]=202. Always significantly lower values than in heathy people, n[82,83] = 184.

Table 2.2 (following). Observed data in healthy and cancer patients

Metric	Daytime peak	Healthy + n[ref]		Cancer patients + n[ref]	
pNN50	**3 AM84**	**12±10 ms (n[71] = 543)**	**No data.**	**No data.**	**Leukemia 16 ± 5ms, n[82] = 36.**
HF	5 AM[68]	13 n.u (men) ($n_{[}^{85}{}_{]}$ = 979) 16 n.u (women) ($n_{[}^{85}{}_{]}$ = 1117)	975±203 ms² and 29±3 n.u ($n_{[6]}$ = 228). 657±777 ms² and 40±10 n.u ($n_{[}^{72}{}_{]}$ = 21.438)	Breast cancer: higher baseline resting HF significantly predicted longer survival, HR=0.75 CI_{95}=[0.60-0.92].[86] HF power significantly associated with longer time to death in hepatocellular carcinoma.[19] lnHF power significantly associated with longer 7-day survival in non-lung cancer.[87] No significant association between frequency domain parameters and survival in advanced cancer.[21]	No statistical difference in HF: metastatic cancer 135.4±186.4 ms², $n_{[18]}$ = 61; control (non-metastatic) 185.3±219.4 ms², $n_{[18]}$=63. Lower lnHF 3.55±2.61 ms², $n_{[}^{74}{}_{]}$ = 103 in low grade cancers and lnHF 2.61±1.18 ms² in high grade cancers $n_{[}^{74}{}_{]}$ = 50. Lung cancers (7 days survival): lnHF = 0.92±2.26 ≤ 7 days, $n_{[}^{87}{}_{]}$ = 29; lnHF = 2.25±3.07 > 7 days, $n_{[}^{87}{}_{]}$ = 109.

Table 2.2 (end). Observed data in healthy and cancer patients

Metric	Daytime peak	Healthy + $n_{[ref]}$		Cancer patients + $n_{[ref]}$	
LF/HF Ratio			**2.8±2.6 ($n_{[}^{72}$] = 21.438)**	Metastasis do not affect HF/LF ratio.[18] Brain tumor: no difference in LF/HF.[88]	No statistical difference in LF/HF ratio: metastatic cancer 1.60±1.83, $n_{[18]}$ = 61; control (non-metastatic) 1.87±1.36, $n_{[18]}$ = 63.
DC		6.5±2.0 ms ($n_{[}^{65}$] = 65) 7.2 ms ($n_{[}^{89}$] = 212)	12.40±5.46 ms ($n_{[}^{90}$] = 191)	Poor prognosis for DC ≤ 2.3 ms, $n_{[53]}$ = 39 Poor prognosis for DC ≤ 4.5 ms, $n_{[}^{91}$]=140	Patients who died within the hospital, survivors DC ≤ 4.0±2.6 ms and non-survivors DC ≤ 2.6±1.8 ms, $n_{[}^{91}$] = 140. Patients who died within 180 days, survivors DC ≤ 4.3±2.9 ms and non-survivors DC ≤ 3.3±2.0 ms $n_{[}^{91}$] = 140

AM: Ante Meridiem; CI: Confidence Interval; *DC :Deceleration Capacity of heart rate; HF: High Frequency; HR: Hazard Ratio; HRV: Heart Rate Variability; LF: Low Frequency; lnHF: natural logarithm of High Frequency; min: minimum; max; maximum; ms: millisecond; NSLC: Non-Small-cell Lung Cancer; n.u.: normalized unit; PM: Post Meridiem; pNN50: NN intervals more than 50 ms; PSA: Prostate Specific Antigen; rMSSD: square root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals; SDNN: Standard Deviation of all NN intervals*

Most of HRV analyses in cancer patients are short-term HRV measurements and focus on solid cancers. SDNN appears to be a relevant marker of survival, although not a pure vagal metric. SDNN in healthy individuals is found around 50 ms, whereas it varies between 7.6 ms and 70 ms (mean=21.65±16.78 ms) in cancer patients, depending on study.

rMSSD seems to be a relevant cardiac vagal marker, but a poor prognostic one. Data show higher rMSSD values in healthy individuals (mean=42±15 ms) than in cancer patients (mean=23.79±20.48 ms, [range 11.5-32.34ms]). pNN50 is also a relevant cardiac vagal marker, but data are scarce.

In the Frequency domain, HF represent a partial measure of vagal tone, and its role in cancer prognosis is uncertain. While reference measurements in healthy patients range from 657±777 ms^2 to 975±203 ms^2, these values are lower in cancer patients (185.3±219.4 ms^2 in non-metastatic cancers and 135.4±186.4 ms^2 in metastatic cancers). Same is observed for LF/HF ratio, with 2.8±2.6 in healthy patients while 1.87±1.36 for non-metastatic cancer and 1.60±1.83 for metastatic cancer patients. Finally, DC appears to be an interesting prognostic and cardiac vagal marker, although further studies are mandatory to confirm these results. In healthy patients, DC has been evaluated at 12.40±5.46 ms. In cancer patients, it may be a prognostic indicator when values fall below ≤4.5 ms.

On metastatic cancers, effects of treatments such as chemotherapy and radiotherapy could be reduced [92] and vagal activity could play a greater role [17]. This may explain the recent interest in the role of the vagus nerve in the prognosis of metastatic cancer [17,23,24]. In the future, this could represent a complementary therapeutic strategy for these cancers.

2.5. External factors' influence

Several external factors could affect the HRV metrics and induce confounding effects. For example, age and sex affect HRV parameters. Globally, higher values in males than females are observed for all ages [93]. rMSSD and pNN50 show a U-shape distribution along the ages (lowest value around 53 yo and an increase over 60 yo). To the contrary, estimators describing whole ANS, as SDNN, linearly decrease with age [71]. However, Acharya et al. [94] found that all metrics display a linear decrease until 55 yo, then linearly increase from 60 yo.

Other factors can affect HRV: health status, food [95], water consumption and bladder filling [96], as well as genetics, body mass index, coffee consumption, smoking, drugs, chronic diseases, etc., [97] or fatigue [98]. To limit these factors' influence, some authors recommend to take measurements in supine position early in the morning [99].

Physical activity (Table 2.3) globally stimulates cardiac vagal activity in healthy and cancer patients as well, even though not all activities have the same effect and HRV metrics. Endurance sports and breathing-related sports like apnea improve HRV more than resistance training sports. Consequently, training programs should pay particular attention to endurance sports.

Table 2.3. Physical activity's effect on HRV metrics in healthy and cancer patients

Population	Ref.	Metric	n	Effects
Healthy				
Midage patients (mean = 67.8 yo)	[100]	SDNN, rMSSD, HF	289	↑ except for resistance training
High level athletes, Young adults	[101]	RMSSD, HF	87	↑ with HIT
		LF/HF ratio	87	↓ with HIT
Student athletes, Students	[102]	Time-domain (men), Time and frequency domain (women)	200	↑ except SDANN in men and SDNN + LF/HF ratio in women
Professional freedivers	[103]	All HRV metrics	13	↑
Elite freedivers + less-trained patients	[50]	rMSSD	5+5	↑ during SA
Cancer				
Colorectal, lung, breast, genital, gastrointestinal, and hematological	[104]	SDNN, rMSSD, HF, LF	146	↑
		LF/HF ratio	146	↓

HF: High Frequency; HIT: High Intensity Training; HRV: Heart Rate Variability; LF: Low Frequency; rMSSD: square root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals; SA: Static Apnea; SDANN: Standard Deviation of the 5 minute Average NN intervals; SDNN: Standard Deviation of all NN intervals

Drugs are the factor leading to the highest variability in HRV in the midage patients [97]. Alpha-1 blockers, Benzodiazepines, Beta blocker, Bupropion, Clozapine, Cocaine, Fanatrex, Flecainide, Scopolamine, Thioridazine, Tricyclics, etc., globally affects HRV [105]. A vagal neuropathy has been observed in male chronic alcoholics [106]. Overall, drugs acting on the heart tend to stimulate vagus nerve activity, whereas psychotropic drugs, sedatives, and antidepressants decrease CVT. Few data are available for radiotherapy, but it tends to decrease DC, rMSSD, SDNN, LF, and HF while it increases AC and FC [107].

Chemotherapeutic agents also appear to reduce CVT. However, current studies do not indicate whether these effects remain long-term and further studies should be done. Table 2.4 focuses on chemotherapy's effects on HRV metrics. Despite these effects, HRV metrics are not systematically measured before therapies. While some studies have estimated metrics before therapies,[73] others measured it during [108,109] or after [110] chemotherapy. To minimize the drug's influence, it seems advisable to take measurement before starting treatment and, during follow-up, before each new chemotherapy session.

Table 2.4. Chemotherapy's effect on HRV metrics in cancer patients

Cancer type	Ref.	Metric	n	Effects
Lung	[108]	LF/HF ratio	12	Higher fatigue correlate with higher LF/HF ratio during sleeping time
Breast	[109]	SDNN	44	↓
Breast	[111]	All HRV metrics	40	↓ non-significant with high-dose of chemotherapy
Breast	[110]	rMSSD, pNN50, HF, LF	20	↓

HF: High Frequency; HRV: Heart Rate Variability; LF: Low Frequency; pNN50: NN intervals more than 50 ms; rMSSD: square root of the Mean of the Sum of the Squares of differences between adjacent NN intervals; SDNN: Standard Deviation of all NN intervals

All other external factors' effects on healthy patients are resumed in Table 2.5, but no data on patients with cancer are available for caffeine, alcohol, and tobacco. However, considering the

significant impact they have on HRV metrics in healthy patients, they have to be taken into account as possible confounding factors in cancer patients. Indeed, in healthy patients, lifestyle seems to influence HRV metrics. Alcohol and tobacco affect all HRV markers, even in regular users. Although less expected, the observed influence of diet, nutrients and fasting implies that these factors should be considered therapeutic factors. Fasting combined with chemotherapy has already shown encouraging results [112]. To the contrary, caffeine's effects are less clear, and call into question about the sympathetic influence usually attributed to it.

Table 2.5. External factors' effect on HRV metrics in healthy patients

Factor/Population	Ref.	Metric	n	Effects
Caffeine				
All patients (regular or non- regular consumers)	[113]	rMSSD, HF	77	↑ with caffeinated espresso in habitual consumers
		LF/HF ratio	77	↓ with caffeinated espresso in habitual consumers
All patients	[114]	SDNN, rMSSD	62	↑ (one study) or ↓ (one study)
		pNN50	10	↓ (one study)
		HF	89	↑ (only one study found ↓)
		LF	18	↑ (2 studies)
		LF/HF ratio	95	↑ or ↓ depending on study
Regular young consumers	[115]	All HRV metrics	30	No effect
Alcohol				
All patients	[116]	rMSSD, SDNN, HF	12	↓
All patients (acute effect)	[117]	HF	133	↓ (8 studies) ↑ (1 study no change)
		LF	98	↓ (2 studies) ↑ (2 studies) and 2 studies no change
Non-alcohol dependent consumers (healthy)	[118]	SDNN	28	↓
		rMSSD	196	↓

Table 2.5 (following). External factors' effect on HRV metrics in healthy patients

Tobacco				
All patients (acute effect)	[119]	SDNN, rMSSD, HF	15	↓ during the next 5 to 10 minutes
		LF, LF/HF ratio	15	↑ during the next 5 to 10 minutes
Mediterranean Diet				
All patients	[120]	All HRV metrics	276	↑
Fish consumption				
All patients	[121]	SDNN (short-term), rMSSD (short+long-term), HF, VLF	4263 (ECG), 1152 (24h Holter)	↑
		LF, LF/HF ratio	4263 (ECG), 1152 (24h Holter)	↓
All patients	[122]	rMSSD, HF, SDNN	157	↑ with increased DHA and increased DHA+EPA.
Vitamine D				
All patients	[123]	SDNN, rMSDD, pNN50, HF	24	↓ in deficient group
		LF, LF/HF ratio	24	↑ in deficient group
All patients	[124]	HF	13	↑
Fasting				
All patients	[125]	SDNN, rMSSD, pNN50	80	↑

DHA: DocosaHexaenoic Acid; ECG: Electrocardiogram; EPA: EicosaPentaenoic Acid; h: hour; HF: High Frequency; HRV: Heart Rate variability; LF: Low Frequency; pNN50: NN intervals more than 50 ms; rMSSD: square root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals; SDNN: Standard Deviation of all NN intervals; VLF: Very Low Frequency

Influence of breathing simulation is highly debated and no consensus exists. Breathing seems to globally increase HRV in healthy patients, while it could be more variable depending on disease. On healthy patients, slow breathing [126], short apnea [127], and controlled breathing [128] would increase LF, LF/HF as well as slow and controlled breathing would increase SDNN and rMSSD, respectively. To the contrary, slow and controlled breathing would decrease HF, while short apnea will decrease rMSSD.

2.6. Collecting data

The main objective is to collect data that reflects CVT properly. To achieve this goal, several points must be addressed: recording duration, measurement tool, analysis software, and artifact corrections.

2.6.1 Recording duration

Several durations are found in literature: long-term (24 h, sometimes 1 to 24 h), short-term (5–10 min, sometimes 2 to 30 min), ultra-short term (10 s to 2 min). The same duration of 2 min could be called short-term and ultra-short-term depending on studies.

Some authors, such as Heathers [96], consider that the measurement must last for at least 1 hour. Frequency analysis from short-term recordings to characterize ANS state or sympathicovagal balance would be problematic. Indeed, a large variation in HRV during measurement can be observed [72]. Others consider short-term recording data to be sufficient [129]. The rMSSD appears to be a reliable metric for assessing HRV from even ultra-short ECG recordings (1 minute or 10 seconds), but the SDNN does not [130,131]. Moreover, the reliability of ultra-short term measurements may contain a small percentage of error due to extraneous physiological influences, particularly respiratory [132]. Currently, to obtain a measurement as reliable as a 24-hour measurement, the reference guidelines recommend 5 to 10 minutes of measurement [4,6].

In unhealthy patients (especially heart disease or mental illness), no consensus exists as well. Munoz et al. [133] mention that long-term recording is not necessary to obtain accurate measurements of rMSSD and SDNN. Others indicate that short-term HRV recording is related to long-term (24-hour) measurements in patients at risk for sudden cardiac death [134].

Patients with cancer. Short-term is the most frequently used time duration in oncology [17,23,24,135]. De Couck et al. [17] advise a minimum duration of 5 minutes to reduce methodological bias.

2.6.2 Measurement tools

The 24-hour ECG remains the reference material [11]. However, the Polar H10 chest belt has been validated against the ECG gold standard at rest and during exercise [136].

Patients with cancer. Only Polar S810i has been used in a published oncology study [81]. However, some current studies used Polar H10 too, such as Martinez et al.[137] ECG is the most commonly used material (sometimes with Lead II configuration [86]), with a short-term Holter-ECG [17-20,23,24,73-75,86,87,135] or ultra-short term ECG [17,23,24,30,75-78].

2.6.3 Analysis software

Several software allow ECG analysis: HRVAnalysis, ECGLab, le HRV Toolkit, RHRV, KARDIA, POLYAN, Artiifact, Codesna, and Kubios HRV. Few software comparisons have been conducted, especially to compare various software to Kubios [138], which is considered as the reference for research purpose and should be preferably used. In addition, Kubios displays Frequency domain metrics obtained from FFT and AR methods. Some measurement tools include analysis software. For example, Synescope Spiderview is included with the spiderview Holter-ECG [139].

2.6.4 Artifact corrections

Artifacts may appear when the recording tool detects missing, extra, or misaligned beats as well as ectopic beats such as premature ventricular contractions (PVC) or other arrhythmias. Artifacts may be caused by electrical interference due to bad contact or external disturbances [105]. Fig. 2.2 highlights differences between a normal ECG and an ECG with artifacts.

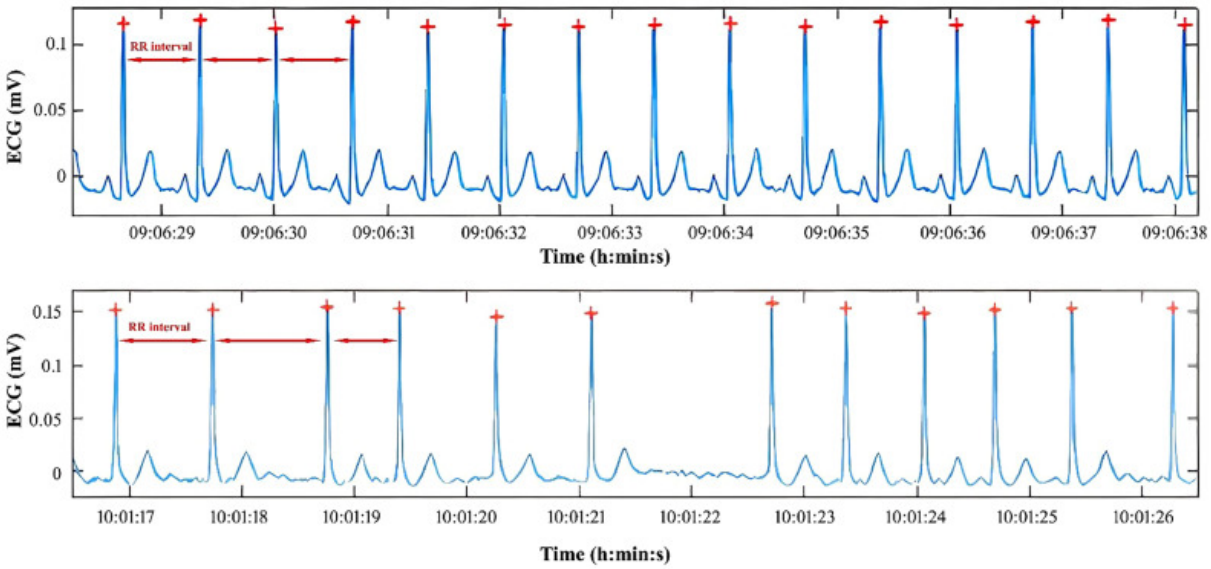


Fig. 2.2 Differences between normal ECG (top) and ECG with artifacts (bottom). ECG, electrocardiogram.

Ectopic beats are the most frequent cause of artifacts [140]. Its can be generated by external factors (sighing or coughing for example) as well as by circadian rhythm, physical or emotional stress [4,141], or cardiac diseases [142]. Treatments, in particular chemotherapy, can induce arrhythmias as well [143-145]. Patient movements can also introduce ectopic beats [105].

Only a few ectopic beats are enough to bias the HRV analysis, and even only one in a short-term recording of 2 min[4] or 10 min [146]. 1% of ectopic beats can significantly affect most of HRV metrics and 0.1% is sufficient to modify rMSSD measurement [147]. They can also mask physiological beats [148,149].

Therefore, non-physiological beats that are not generated by sinus node depolarization must be eliminated from the recording [150]. As opposed to non-physiological artifacts caused by cough and movement, the ectopic beats have to be included. The regularity of the beats, the interval between them and their amplitude has to be visually checked to determine which ones must be excluded from the analysis [6,10,11,151,152]. It is advised that analyses always be performed by a single trained investigator [153]. Catai et al. [154] published guidelines and procedures for HRV analysis.

For Sheridan et al. [155], up to one third of the beats could be deleted in a short-term duration (1 min) to measure rMSSD and SDNN without impacting the whole HRV measure by more than

5%. Others suggest that SDNN and rMSSD are not affected at all with a loss of 2.5% of data [156].

Consequently, several adjustments are possible [157]: **Uncorrected** (no correction applied to any intervals; data were left as recorded), **Deletion** (erroneous RR interval[s] were deleted from the recording), **Interpolation** (erroneous non-normal RR intervals are replaced by interpolated intervals), **Degree Zero** (substitution of artifact[s] with a mean value calculated from surrounding R-R intervals), **Degree One** (a straight line is drawn over the irregular intervals to obtain new values), **Cubic** (cubic interpolation uses four datum points to compute the polynomial; no constraints on the derivatives), **Spline** (cubic spline interpolation that computes a third order polynomial from only two datum points with the additional constraint that first and second derivatives at the interpolation points are continuous).

HRV analysis software offer automatic adjustment. For example, Kubios provides options for the detection and correction of ectopic beats and artifacts, with several correction modes depending of the sensitivity threshold (in second): very low 0.45 s; low 0.35 s; medium 0.25 s; strong 0.15 s; very strong 0.05 s; and custom threshold [158]. While using medium and strong corrections, Kubios displays fewer errors than other software such as Polar Protrainer 5 or Macalester. However, Alcantara et al. [159] suggest the lowest Kubios filters (very low, low, or medium) in younger populations and a stronger one in older populations (strong). In any case, the very strong Kubios filter has to be used with caution.

Kubios offers an automatic beat correction algorithm which seems to be the most accurate [160]. However, Laborde et al. [10] warn that this correction may detect physiological beats as artifacts. This can bias the whole HRV analysis. Kubios indicates that only two artifacts in the 5-minute analysis recording have a significant effect on HRV parameters, as previously noted. Nonetheless, Kubios specifies that less than 5% should be removed to avoid suppressing variability [158].

2.7. Suggested protocol to evaluate cardiac vagal tone in oncology

Our review aims to offer clear and easy-to-use guidelines to properly evaluate CVT. We previously described all confounding factors that would bias HRV measurements and analysis,

focusing on patients with cancer and undergoing chemotherapy treatment. The following seven key points below will help to considerably reduce errors in HRV analysis.

Key points:

- **Confounding factors**. No alcohol two hours before recording and no nicotine 10 minutes before recording [116,117,119]. To minimize the drug's influence, we recommend taking measurement before starting chemotherapy treatment, during follow-up, and before each new chemotherapy session.
- **Breathing**. Spontaneous breathing is the better breathing protocol. Measurements with respiratory stimulation (biofeedback for example) are not easy to perform due to the systemic state of patients with cancer and undergoing chemotherapy [36,143-145]. However, if the respiratory stimulation does not produce too many artifacts, it could be used [17].
- **Circadian rhythm**. Recordings should be done in the morning, in a 4 hours interval of time [96].
- **Duration**. Allow the patient to rest for at least 5 minutes in the supine position before measurement. Avoid any recording shorter than 5 minutes in unhealthy patients, especially patients with cancer [6,17].
- **Tool**. Holter-ECG is the reference tool in oncology for HRV measurement [17,23,24,135]. Polar H10 chest belt appears to be the most accurate portable device for HRV recording if a Holter-ECG is not available.
- **HRV metric**. Use rMSSD to estimate the CVT [6]. It has to be combined with other variables such as SDNN for vital prognosis assessment. DC offers interesting prospects for the future as it could lead to less artifacts and may represent a relevant cardiovascular prognostic marker [53]. Kubios can be used for HRV analysis.
- **Artifacts**. Select R-R interval sections without artifacts. If it is not possible, artifacts must be corrected or removed [11,105,152]. They have to be visually identified by a trained investigator.[6,10,11,151] Automatic beat correction algorithm is not recommended.

2.8. Conclusion

Literature provides complex and spread data about HRV and confounding factors. Our review proposes a checklist of key points to properly measure HRV in oncology, in an easy-to-use way.

These simple recommendations can be followed in clinical practice as well as in clinical research to assess the CVT. An important key point is that, even if SDNN appears as a better predictor of survival for patients with cancer [17,23,24], the rMSSD is the most specific estimator for the CVT (especially in short-term measurement).

By identifying and synthesizing the confounding factors that can affect HRV metrics, targeted therapies to improve HRV in cancer patients can be more easily implemented. For example, physical activity is used in some medical departments to improve patients' global health and quality of life, and in a same approach, it would be possible to organize HRV stimulation protocols in routine practice to improve vital prognosis. To evaluate the effectiveness of such protocols, clinical trials have to be carried out by controlling the confounding factors, with controlled food, physical activity with apnea, reduction of certain drugs (not essential to the treatment), tobacco, or alcohol. Just for your information, non-linear methods were not considered at the time of writing due to the limited information and studies available, but they will be taken into account in future work. Our review would be helpful for future clinical trials. Having established a rigorous protocol for measuring CVT in oncology, the next logical question is: which interventions are genuinely capable of modulating it? Osteopathic practice represents one candidate, given its known influence on autonomic tone through manipulative treatment. However, it is often claimed that the diagnostic procedures themselves – the listening tests – already alter autonomic markers. In Chapter 3, we directly investigated this question.

3. Chapter 3: Can osteopathic tests influence heart rate and heart rate variability?

This Chapter is essentially drawn from:

Gillet F, Gault M, Dussault V, Cheggour S, Grinand M, Martinez P. Impact of osteopathic tests on heart rate and heart rate variability: an observational study on osteopathic students. J Osteopath Med. 2025 Mar 3. doi: 10.1515/jom-2024-0240.

General abstract and Key Points of the Article:

This article is part of my thesis as it would have allowed me to acquire methodological and supervisory skills:

- Training students in protocol development and the use of HRV measurement tools,
- Training students in the different HRV metrics,
- Analyzing HRV measurements (+200 tracings analyzed) from healthy individuals,
- Interpreting results and the impact of manipulations on HRV,
- Supervising and mentoring students throughout a project for 2 years until publication.

The article highlights that osteopathic tests do not, contrary to what is often conveyed, cause variations in HRV.

3.1 Introduction

Osteopathy is a care method based on the therapeutic actions of osteopathic manipulation [161]. Before treatment, an osteopathic physician performs a physical and structural examination to assist in diagnosis and treatment [162,163]. Touch, a key communication tool in manual therapies, helps to identify somatic dysfunctions [162]. It provides the initial physical contact that patients expect and appreciate in manual therapies [164]. Touch can serve different purposes, such as providing therapeutic intervention or gathering information [165]. Touch can also play a role in reducing negative emotions, decreasing stress biomarkers [166], and increasing relaxation and feelings of safety [167]. During osteopathic training, students progressively develop their sense of touch and learn various diagnostic techniques, including osteopathic listening tests. These

tests are introduced early in the curriculum and continue to be refined throughout their education, forming part of their diagnostic toolkit [168]. Regarding the physiological basis of listening tests, the work of Biel et al. [169] on the reproducibility of palpation and Vincent et al. [170] on the quantification of tissue responses provide essential insights into the reliability of listening tests in osteopathy. Listening tests in osteopathy rely on the osteopath's ability to perceive information transmitted by mechanoreceptors and proprioceptors, which detect mechanical changes in tissues, such as pressure and movement [171]. Additionally, research by Bland et al. [172] on the thixotropy of tissues adds an important dimension to understanding tissue responses during these tests. Research on the ANS has highlighted the impact of osteopathic manipulative treatment on its function. The ANS, which regulates involuntary bodily functions, comprises the sympathetic (SNS) and parasympathetic (PNS) systems. These systems influence heart rate (HR) and HRV, both of which serve as markers for ANS activity [173]. HR, measured in beats per minute (bpm) [174], reflects ANS activity, increasing with SNS dominance and decreasing with PNS activation [175,176]. It is a straightforward marker that can reflect potential influences of osteopathic interventions on the ANS [176]. For instance, C.E. Henley's study demonstrated parasympathetic activation during cervical myofascial release [177]. HRV, which measures the variability in time between successive heartbeats, provides deeper insights into ANS function. The rMSSD, a time-domain HRV measure, reflects vagal tone (PNS activity) and is independent of breathing rate [178,179] and measured in milliseconds (ms) [174]. Frequency analysis of HRV, using the low-frequency/high-frequency (LF/HF) ratio, is also a reliable measure, provided the analysis lasts at least five minutes [180]. RMSSD reflects vagal tone (PNS activity), while the LF/HF ratio measures sympathovagal balance [178,181].

In this study, rMSSD serves as the primary marker for CVT, while HR and the LF/HF ratio are secondary measures. The objective is to determine whether osteopathic listening tests, widely taught but underexplored in terms of physiological effects, induce measurable changes in these markers. Specifically, do HR and HRV significantly change during a listening test session? Beyond their diagnostic role, could these tests elicit physiological responses in the patient?

3.2 Methods

This observational study was carried out from November 2022 to February 2023. It took place in the clinic of an osteopathic school. The study investigates the effect of listening tests. A protocol of these tests on the right knee, the digestive system and the cranium was realised. A

protocol of these tests on the right knee, the digestive system, and the cranium was carried out. These areas were chosen to explore the three main fields of osteopathy: musculoskeletal, visceral, and cranial, which have shown the effects of osteopathic manipulative treatment on heart rate and heart rate variability in prior studies [182-185]. Data on heart rate**,** rMSSD, and LF/HF ratio were collected from subjects before and after a listening test session and compared with those from a control group. A third group, involving light pressure application without therapeutic intent, was also included as a placebo. In the light pressure group**,** an object simulating light touch pressure (0.8 newtons [N], equivalent to 81.58 grams [g]) was used [186], it has no therapeutic intent [187]. In the protocol, it is materialised by an object close to the weight defined for light touch, i.e. 0.8 newtons (N), which is equivalent to 81.58 grams (g) [186]. To isolate the effect of human contact, no practitioner touch was involved in this group. The control group participants underwent no interventions but were asked to lie on their back for the same duration as the other groups.

3.2.1 Population

A total of 51 participants, recruited on a voluntary basis, were selected from osteopathy students (first to fifth year). An intervention was carried out before a class to introduce the study. The project was explained to them as a heart rate study, without mentioning the listening tests so that they wouldn't know the different groups. The non-inclusion criteria were also presented during this intervention. Several factors can influence HR and HRV, potentially affecting the results:

- Consumption of coffee or energy drinks in the past 24 hours [178,188-190].
- Participation in sports within the last 24 hours [178,191,192].
- Smoking any type of cigarette, including e-cigarettes, in the last 20 minutes [191,193-195].
- Presence of known cardiac pathology, as treatment may influence HRV measurements [196].
- Having an acute illness (e.g., cold, fever), which contraindicates osteopathy [197].
- Cardiac and non-cardiac comorbidities, as their treatment may affect HR [198].
- Use of anti-hypertensive, antidepressant, antipsychotic, or beta-blocker medications within the last 48 hours, which can impact HR and HRV [178,199,200].

Volunteers were contacted by email or phone number and an appointment was scheduled. Students were asked to complete an informed consent form, according to French regulation. They also completed a document to affirm that they didn’t present a non-inclusion criterion.

If the participant didn't provide informed consent or had a non-inclusion criterion, he wasn't selected for the study. For those selected, tests were carried out, in a single session. Participants with too high artifacts rates during the software analysis were excluded. The percentage of ectopic beats considered too high for HRV measurements was greater than 1%, and greater than 0.1% for rMSSD [201,202].

3.2.2 Randomization

The repartition between the osteopathic test group (OTG), light pressure group (LPG) and control group (CG) were done by blocks of six on Excel. Participants remained unaware of the existence of other groups to reduce bias. Demographic information for each group is presented in Table 3.1 below.

Table 3.1: Demographic information in osteopathic test group, light pressure group and control group

	Osteopathic test group	**Light pressure group**	**Control group**
	Mean (SD) or %		
Sex (% Male / Female)	29.4 / 70.4	23.5 / 76.5	23.5 / 76.5
Age (years)	21.6 ± 1.5	21.8 ± 1.5	21.8±1.6
18	5.9	11.8	5.9
19	11.8	5.9	11.8
20	17.6	23.5	11.8
21	23.5	11.8	23.5
22	29.4	35.2	23.5
23	5.9	5.9	11.8
24	5.9	5.9	11.8

Each test session involved three investigators: one performed the tests, another reproduced the protocol, and a third conducted the measurements. Investigators rotated roles randomly between participants to further minimize bias.

3.2.3 Protocol

The protocol was conducted in a room with controlled ambient temperature to prevent environmental variations that could influence HRV [201].

The protocol for each group, with the number of participants at each stage, is summarised in a flow chart, shown in Figure 3.1 below:

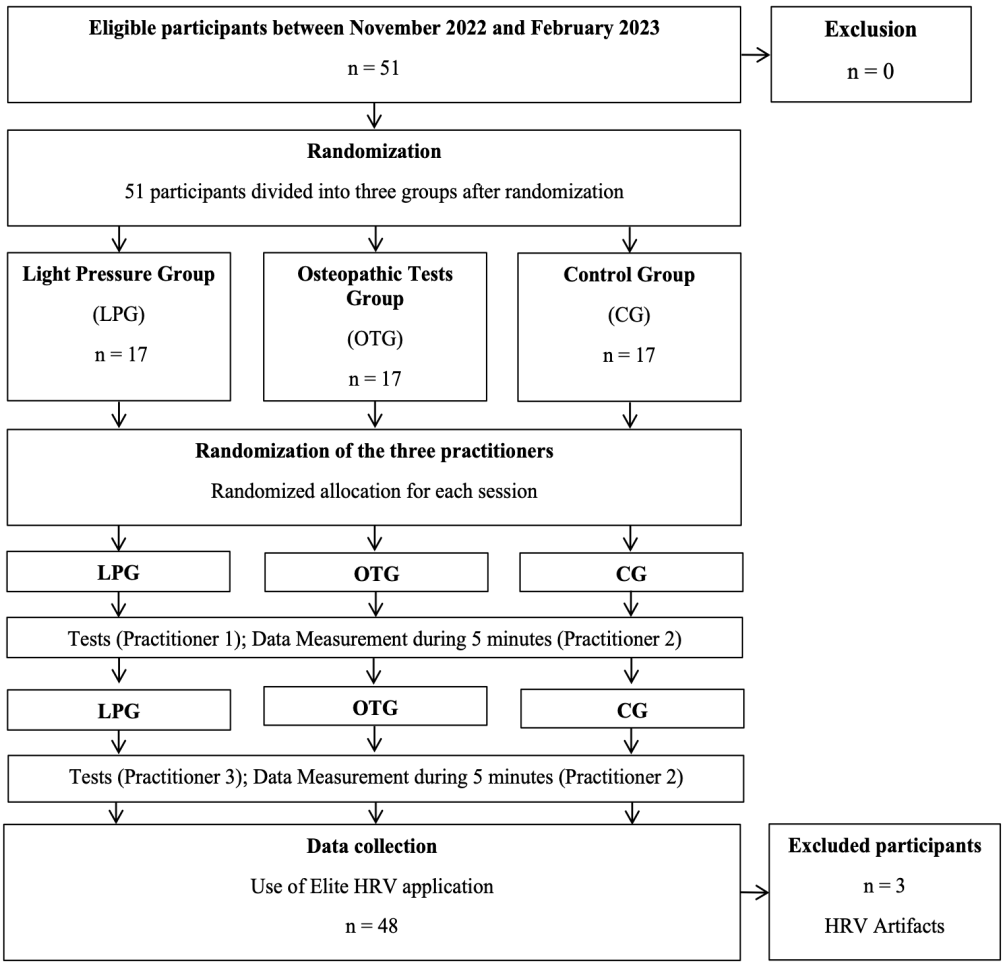
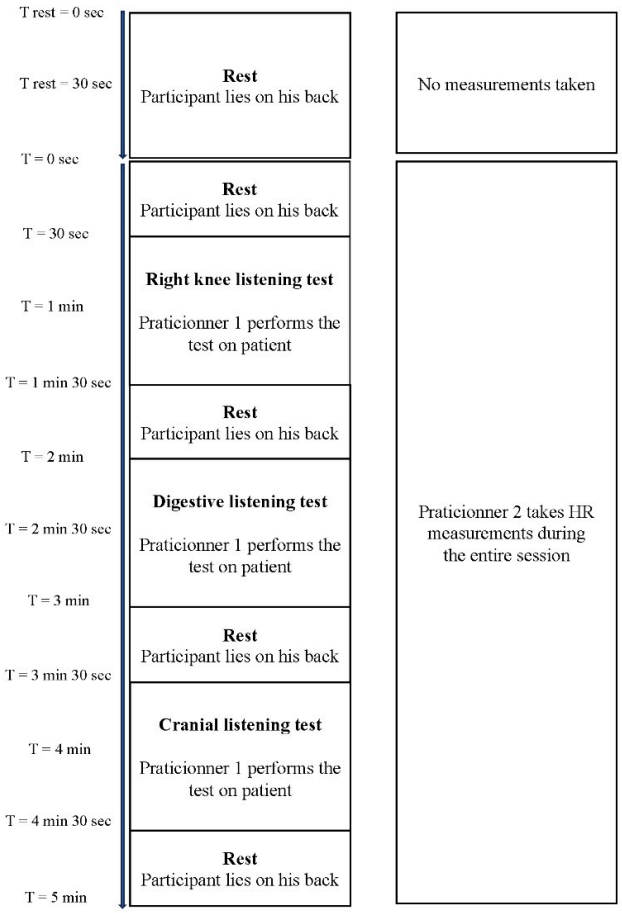


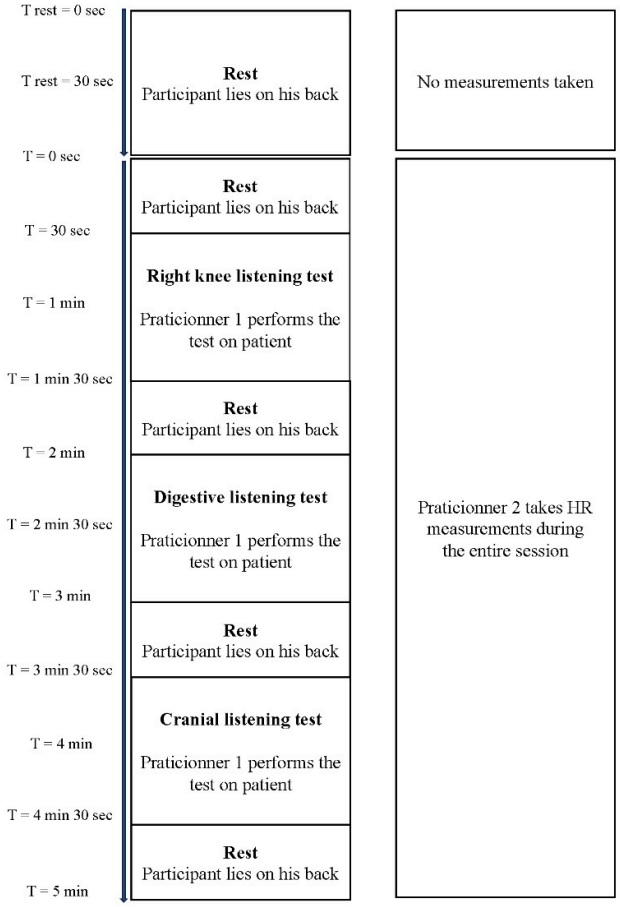
Figure 3.1: Flow chart for the observational study. *HRV: CG: control group; Heart Rate Variability; LPG: Light Pressure Group; OTG: Osteopathic Test Group.*

The details of each test session are then explained in Figure 3.2 below for all the different groups:

A.



B.



C.

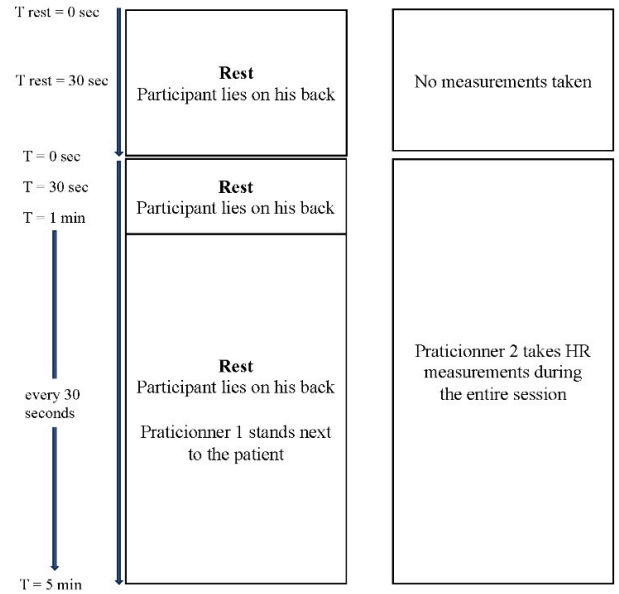


Figure 3.2: Tests protocol for the different groups. A. Protocol for the osteopathic tests group session. B. Protocol for the light pressure group session. C. Protocol for the control group session. *HR: Heart Rate*.

Each test session is described for the first practitioner. The second one reproduces the same protocol. HR : Heart Rate.

The test procedures for each group are summarized below:

- Osteopathic Test Group (OTG):
  The practitioner performed listening tests on the right knee (hands placed on femoral condyles and tibial plates), the digestive system (right hand positioned between the navel and xiphoid appendix), and the cranium (spheno-basilar symphysis with a four-finger grip).
- Light Pressure Group (LPG):
  A rice bag weighing 81.58 grams was placed on the right femoral condyles, the area between the navel and xiphoid appendix, and the forehead, in sequence.
- Control Group (CG):
  Participants lay supine for the same duration as the other groups without undergoing any tests or interventions.

3.2.4 Heart rate and heart rate variability measures

Participants were asked to remain still and silent throughout the measurements, as movement and speech can distort HRV analysis [203]. They lay on their back and rested for one minute before the measurements began. Heart rate (HR) and HRV measurements were then taken over a five-minute period. The tests and light pressures applied to the participants were always conducted with them in the supine position. It has been shown that body inclination increases heart rate[177], which is why no standing or sitting tests were performed.

For each group, a POLAR H10 chest strap was fitted by the first practitioner over the participant's xiphoid process. The size of the strap was adjusted for each participant so that the sensor made contact with the skin. This strap enables non-invasive HR and HRV data collection for the student. The suitability of the strap for use was evaluated against electrocardiogram recordings, and it was recommended for practitioners [202]. Simultaneously, data were collected using the Elite HRV mobile application, software designed for the chest strap [204]. The collected data were then analyzed using the Kubios HRV software, which allows the study of HR,

rMSSD, and the LF/HF ratio [205]. The validity and reliability of the three tools used were confirmed [179,204,206].

3.2.5 Statistical analysis

The first stage of the statistical analysis was to define if the values follow a normal distribution. The Shapiro-Wilk test was used to study the normality of the values of each measurement criterion. The results show that the HR values follow a normal distribution, while the rMSSD and LF/HF ratio values do not follow a normal distribution.

To begin the statistical analysis, it was necessary to compare the first 30 seconds of each group, for the three selected criteria, to make sure that there is no difference between the three groups at the beginning of the test session. Student's t-test allowed to compare FC values between the three groups. As data are independent, Mann-Whitney test was used to compare the rMSSD and LF/HF ratio of the different groups.

To compare the different averages calculated before and after the protocol, comparison of means tests were carried out. The following tests were used for paired data. Student's t-test was used to compare the HR averages. The Wilcoxon test was chosen to compare the means of the rMSSD and the LF/HF ratio. The significance threshold of the tests chosen is 5%, or $\alpha=0.05$.

3.3 Results

3.3.1 Population

51 participants were selected for the study. They were equally and randomly allocated to the osteopathic test, light pressure or control groups. Each group was thus composed of 17 students, from the first to the fifth year of study (1Y to 5Y). After data analysis with the Kubios software, 3 participants in the LPG group were removed from the study because their values showed a percentage of artifacts greater than 5%.

3.3.2 Main results

After comparing the first 30 seconds between each group, no significant difference was found. The p-values between OTG and CG are p=0,293 for HR, p=0,158 for rMSSD and p=0,811 for

LF/HF ratio. Between the OTG and LPG, they are p=0,315 for HR, p=0,861 for rMSSD and p=0,799 for LF/HF ratio. Concerning the last two groups, LPG and CG, p-values are p=0,968 for HR, p=0,063 for rMSSD and p=0,591 for LF/HF ratio. As there were no difference between the groups from the start, the rest of the statistical analysis could be carried out.

To compare the ANS markers before and after the test sequence, measurements were taken in the first 30 and last 30 seconds of each test session. Each criterion mean with their standard deviation are represented on figure 3.3.

Figure 3.3A shows the heart rate mean before and after the protocol for each group. Figure 3.3B represents the rMSSD means before and after protocol, in the three groups. The same goes for the Figure 3.3C, but with LF/HF ratio mean.

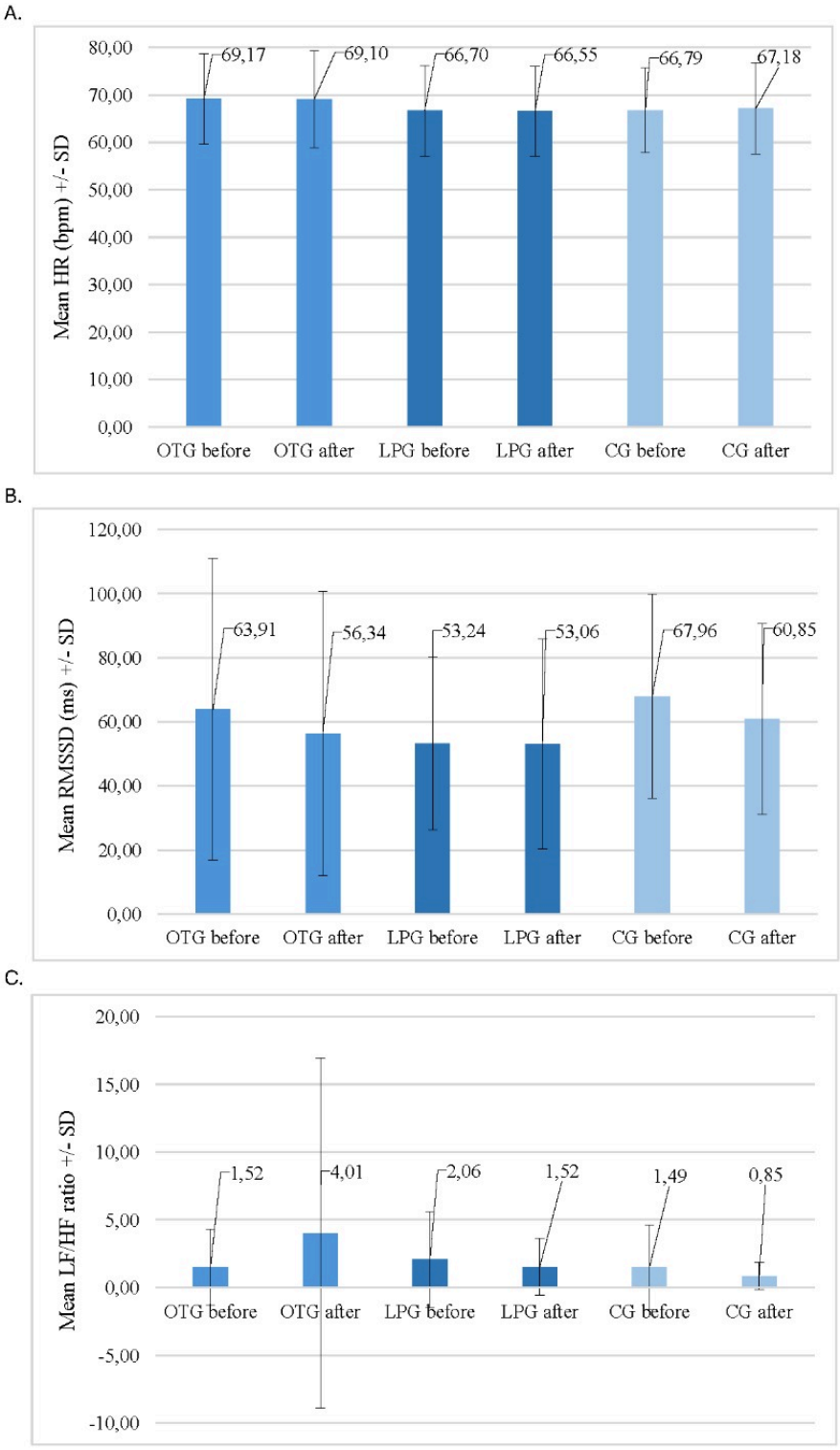


Figure 3.3: Histogram of the means of the different metrics before and after the protocol.

A. Heart rate before and after protocol for each group; B. rMSSD before and after protocol for each group; C. LF/HF ratio before and after protocol for each group. CG: control group; LPG: Light Pressure Group; OTG: Osteopathic Test Group; SD: Standard Deviation.

The values shown on this figure are represented below, for each group.

- Osteopathic test group

Averages with their standard deviation of 30 first seconds of OTG were 69.17±9.58 bpm for the HR, 63.91±47.09 ms for the rMSSD and 1.52±2.80 for the LF/HF ratio. Concerning the last 30 seconds, averages and their standard deviation were 69.10±10.24 bpm for the HR, 56.34±44.44 ms for rMSSD and 4.01±12.93 for LF/HF ratio. When comparison of the means before and after tests, there was no difference significant emphasis for HR (p=0.884), rMSSD (p=0.064) or LF/HF ratio (p=0.106).

- Light pressure group

The light pressure group also showed no significant difference before and after the pressures. The averages and their standard deviation for the first 30 seconds were 66.70±9.55 bpm for the HR, 53.24±26.94 ms for the rMSSD and 2.06±3.55 for the LF/HF ratio. The comparison of averages did not show significant difference for HR (p=0.812), rMSSD (p=0.814) or LF/HF ratio (p=0.981).

- Control group

For the control group, the averages and their standard deviation were 66.70±9.55 bpm for HR, 53.24±26.94 ms for rMSSD and 2.06±3.55 for LF/HF ratio. No significant differences were found in comparisons of protocol start and end averages for HR (p=0.495), rMSSD (p=0.209) or the LF/HF ratio (p=0.675).

3.4 Discussion

3.4.1 Interpretation

The results indicate that there were no significant changes in heart rate or HRV metrics (rMSSD and LF/HF ratio) following the osteopathic listening tests or light pressure application. Therefore, the hypothesis that these tests could influence ANS markers is not supported by the data. The findings suggest that the selected osteopathic listening tests do not have a measurable therapeutic effect on HR or HRV. The results suggest that these tests remain diagnostic tools used by osteopaths to detect somatic dysfunctions rather than interventions that produce

therapeutic effects on the ANS. They do not induce significant changes in HR and HRV, and thus do not have a measurable physiological impact on the markers we selected.

Previous studies have shown that osteopathic manipulative treatment (OMT) can influence the ANS, especially by modulating the sympathovagal balance through HRV metrics like the LF/HF ratio [183]. Another study propose that the HRV as a useful method for developing simulated controls during studies on osteopathic manipulations [177]. While OMT has been associated with changes in HR and HRV, our study's results suggest that listening tests themselves do not elicit similar physiological effects. It would be worthwhile to investigate whether comparing listening tests to actual osteopathic manipulative treatments would yield different results. Future studies could focus on treatment techniques rather than just diagnostic tests to explore their potential effects on the ANS. Regarding the light pressure group, our data show that a simple application of light pressure (using a rice bag without therapeutic intent) did not lead to any significant changes in HR, rMSSD, or LF/HF ratio. This suggests that touch alone, when not combined with a therapeutic intent, does not appear to influence the autonomic nervous system. The lack of therapeutic effect observed in the osteopathic listening tests can be attributed to their primary diagnostic purpose. These tests are designed to detect somatic dysfunctions through palpation and are not intended to provide therapeutic interventions or stimulate physiological changes. Unlike OMT, which involve intentional and targeted interventions to influence physiological processes, the listening tests employ light touch primarily for assessment purposes. Furthermore, the light pressure applied during the listening tests may not constitute a sufficient stimulus to elicit a measurable autonomic response. Studies that have observed changes in HRV following osteopathic treatments often involve more dynamic manipulations that engage the musculoskeletal and nervous systems to a greater extent. In contrast, the listening tests do not involve sustained or intentional therapeutic interventions, which could explain their lack of impact on ANS markers such as HR and HRV. Another factor is the role of intentionality in therapeutic touch. Previous research suggests that the therapeutic intent behind an intervention can influence its physiological effects. In this study, the tests were explicitly diagnostic, and the absence of therapeutic intent may have contributed to the lack of observable changes in HR and HRV. This finding is supported by the results of the light pressure group, where non-therapeutic touch also failed to produce significant effects on ANS markers.

These findings emphasize the need for future studies to distinguish between diagnostic and therapeutic interventions in osteopathy. Investigating the physiological effects of treatment

techniques, rather than diagnostic tests, may provide more insight into the mechanisms by which osteopathic interventions influence the ANS.

3.4.2 Limits

This study has several limitations. Participants were osteopathy students, who were familiar with listening tests and aware of their own group's procedures, but not those of the other groups. Their prior experience with these tests may have influenced their perception of touch compared to the general population. As a result, our sample may yield different results from those that could be expected in the general population. Furthermore, because the participants were not seeking treatment, their readiness to receive touch in a therapeutic context could have been affected [207].

Another limitation is that the practitioners were students. As the quality of palpation improves with training [207-209], it is expected that the quality of touch would differ between practitioners and, moreover, between students and experienced osteopaths. Investigating whether practitioners of different experience levels such as newly graduated osteopaths or students from various years produce different physiological effects could provide useful insights.

The testing protocol followed a fixed sequence (knee, digestive area, and skull), which may have influenced the outcomes. Testing these sequences in different orders could potentially yield different results and insights.

3.4.3 Generalizability

This study is repeatable and reproducible, as the protocol and hand positions for the listening tests are easily replicable by those trained in osteopathy. However, this study could be expanded by exploring other markers of the ANS to provide a more comprehensive understanding of the potential effects of listening tests. HRV is a simple, non-invasive method for measuring sympathovagal balance [210]. By exploring additional HRV metrics, valuable insights could be gained, as HRV is easily measurable and carries minimal risk for participants. Furthermore, a more thorough investigation of osteopathic listening tests is warranted. This could include assessing other physiological markers beyond the ANS to ensure there are no unintended physiological effects that could be attributed to these tests as treatments. Such examinations could serve as important reference points for clinical trials. It would also be interesting to generalize this study to other osteopathic tests. Different physiological markers may yield

different results, and perhaps other osteopathic tests would demonstrate modifications in these markers. The statistical analysis part could also be modified by adding other data as confidence intervals, or other statistical tests that could bring more information.

Finally, the small sample size (17 participants in each of the three groups) may limit the generalizability of the findings. As this is an observational study presenting preliminary results, further investigation with a larger sample size would be an important next step to confirm or challenge these conclusions.

3.5 Conclusion

This study aimed to investigate the impact of osteopathic listening tests on markers of the ANS, focusing on heart rate, rMSSD, and the LF/HF ratio. The primary hypothesis posited that these tests would influence the ANS. However, the analysis of results did not support this hypothesis, as no significant differences were observed in the selected ANS markers before and after the listening test sessions.

To expand on these findings, it would be beneficial to conduct further studies. Previous research has demonstrated the impact of osteopathic manipulative treatment on the ANS [177,183,211], and comparing these effects with those of osteopathic listening tests could provide valuable insights into the differential impacts of testing versus treatment.

The finding that osteopathic listening tests do not measurably alter HRV clarifies the boundary between diagnostic touch and genuine vagal stimulation. It also raises a deeper question: why is the autonomic nervous system so consistently dysregulated in cancer patients in the first place? To answer this, it is necessary to step back from measurement methodology and examine the pathophysiological origins of cancer itself. Chapter 4 proposes a revised framework for carcinogenesis – one that places mitochondrial dysfunction at its center – and that will prove essential for understanding the tumor microenvironment in which vagal activity is suppressed.

4. Chapter 4: Time to reconsider the paradigm of carcinogenesis?

This Chapter is essentially drawn from:

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General abstract and Key Points of the Article:

This article plays a major role in my journey. Indeed, by studying the pathophysiological mechanisms of cancer for nearly a year, it allowed me to gain a deeper understanding of cancer. The article is a hypothetical one based on in vitro and in vivo studies, and highlights that:

- Available evidence seems to confirm that cancer could be a metabolic disease,
- Somatic mutations are non-essential and sufficient,
- Mitochondrial dysfunction could start in a stem cell, leading to the formation of cancerous stem cells,
- Cancer stem cells could be involved at all stages of cancer, from carcinogenesis to metastasis,
- Cancer stem cells also help explain recurrences and therapeutic failures,
- The elements that make up the tumor microenvironment.

All of this knowledge was essential for a biological and metabolic understanding of cancer. This knowledge was subsequently reused in Chapter 6, where the tumor microenvironment is varied, and many signals from it can be captured by the nerve. Thus, in Chapter 6, building on the knowledge gained in this article, we will explore the bidirectional communication between the tumor and the autonomic and central nervous systems (CNS), including the major role of the vagus nerve.

4.1. Introduction

Despite the therapeutic advances of the last century, inter alia, chemotherapy, radiotherapy, and immunology, cancer's incidence and mortality continue to rise. Many theories have been proposed to explain the origin of cancer [212]. In the 1920s, the mitochondrial metabolic theory

suggested that cancer is caused by a disorder in cellular respiration [213],[214]. A few decades later, the discovery of deoxyribonucleic acid (DNA) led to the somatic mutation theory (SMT), hypothesizing that cancer results from an abnormal proliferation of cells generated by the accumulation of mutations (DNA) within a single cell [215]. Another more recent model is the cancer stem cells (CSCs) theory. In the latter model, the CSCs are a small subpopulation of cells within tumors that possess the ability to self-renew, differentiate, and form tumors [216]. Finally, the tissue organization field theory of cancer (TOFT) suggests that cancer is a tissue-based disease and arises in disorganized tissue and not in individual cells [217]. Nowadays, the SMT is the most widespread theory.

It is generally accepted that the environmental and biopsychosocial factors (ecosystem, lifestyle, work environment, home environment, drugs, etc.) play an important role in tumorigenesis [218]. For instance, many traditional communities that follow a hunter–gatherer diet and do not live in industrialized regions have a lower incidence of cancer [219]. Tumorigenesis observed in animal models provides a basis for understanding the mechanisms behind it. Generally, five methods are used to generate tumors: spontaneous mutations, chemical agents/radiation, retroviruses, DNA microinjections, and local or systemic injection of malignant cells [220]. Cancer induction by chemical agents or ionizing radiation is far more effective than by other methods [221]. Yet, the somatic mutation theory may not provide a complete explanation of cancer. For example, mutations in primordial genes have been observed in healthy patients, and a few substances can be carcinogenic without being mutagenic. In the 1920s, Warburg developed an understanding of cancer based on mitochondrial alterations. A few decades later, the introduction of the concept of CSCs furthered the comprehension of cancer development. Our approach aims to combine the two in order to provide supplementary insights into the different stages of cancer development, specifically mitochondrial alterations in CSCs being able to reduce oxidative phosphorylation (OxPhos) efficiency.

4.2. The Somatic Mutation Model Alone May Not Explain Tumorigenesis

The Somatic Mutation Model asserts that a mutated gene is responsible for tumorigenesis. However, there is no evidence whatsoever that identified DNA mutations cause a cell to go from normal to malignant [222,223]. All the cellular events and rearrangements that lead to malignancy remain elusive [224] particularly in the early stages of tumorigenesis [225]. Because of this, in most cases, identifying a specific mutation that initiates tumorigenesis is impossible [226]. Morales et al. [227] have shown that modification of HRAS gene increases fibroblast telomerase

activity, making cells immortal but not causing tumorigenesis. Loss of oncogene expression may not be correlated with suppression of tumorigenesis, suggesting that oncogenes may be an effect rather than a cause of cancer [228]. A recent analysis of the data shows that almost all genes could be associated with cancer [229]. Tumor DNA sequencing data have shown that cancer cells have multiple heterogeneous DNA mutations [222]. Mutations may even be heterogeneous between tumors within the same cancer category [230]. A tumor is genomically heterogeneous, with each cell having a different mutational signature[231]. The SMT theory suggests that tumorigenesis arises from a series of somatic mutations, perhaps at key points in the genome. This would result in a pattern of mutations shared by the genomes of all cancer cells. However, the observed heterogeneity invalidates the existence of a mutational pattern. Considering that somatic mutations may be a consequence rather than a cause, genome heterogeneity would be better explained by combining SMT with other factors described in the MSCC theory. It becomes difficult to determine a causal mechanism with SMT concept, especially with tumors where we can find more than 10,000 mutations in tumor cell gene exons[232]. On the other hand, many genes defined as cancer driver genes have been found in normal, healthy cells [233-239]. These mutations even appear in important genes like KRAS and even TP53, known as the "guardian of the genome" [240,241]. The TP53 gene also appears mutated in diseases other than cancer, such as rheumatoid arthritis [242-244]. The most frequently mutated gene, TP53, appears mutated in only 35% of all cancers [245]. Moreover, some carcinogens do not always cause mutations [246-248] and this seems to contradict the theory. Non-genotoxic carcinogens could cause cancer by modifying the endocrine system, inducing cytotoxicity, increasing inflammation, suppressing the immune system, and causing oxidative stress [247]. Several inert substances, such as plastics, when implanted in the tissues of sensitive animal hosts, induced tumors locally [249]. For example, substances such as methapyrilene, hexachlorobenzene, chloroform, p-dichlorobenzene, and d-limonene could result in a tumor even if they do not release genotoxic compounds that induce mutations in candidate genes (oncogenes, tumor suppressor genes) [250]. Overall, the criteria for establishing a causal link between the somatic mutation theory and cancer are rarely met [251]. Therefore, in the light of the evidence provided, somatic mutation could be a consequential and subsequent phenomenon occurring after the onset of tumorigenesis [252].

4.3. Role of Mitochondria in Tumorigenesis

Mitochondria are complex organelles that influence cancer initiation, growth, survival, and metastasis [253,254]. Known carcinogens can cause mitochondrial dysfunction, especially chemical

agents/drugs [255-257], radiation [258], and viruses [259]. Thus, mitochondrial damage may precede tumorigenesis [260]. Mitochondrial dysfunction is associated with altered metabolisms and can promote tumorigenesis as well as metastases [261]. Mitochondrial DNA (mtDNA) mutations have been reported in all cancer types [262,263] and are a major source of driver mutation in cancer [264,265]. However, like somatic mutations, it is not sufficient enough to explain all cancers. Indeed, no pathogenic mtDNA mutations were found in five mouse brain tumors [266]. So, it seems that genetic mutations are not the cause of cancer, even in mitochondria, unless they can cause a chronic reduction in the efficiency of OxPhos [267]. Cancer may result from progressive disruption of adenosine triphosphate (ATP) synthesis by OxPhos, leading to compensatory ATP synthesis [214]. Pedersen synthesized data from over twenty studies showing that no highly malignant tumor had normal mitochondria in number and morphology. The total number of mitochondria in tumor cells was significantly lower than in healthy cells, and the total respiratory capacity of tumor mitochondria was lower than in healthy cells [268]. The degree of malignancy could be directly correlated with the degree of mitochondrial structural abnormalities [269]. It has been shown that human cancers exhibiting structural alterations in mitochondria cristae can suffer from swelling and partial or total cristolysis [270,271]. Evidence suggests that various cancers exhibit abnormalities in mitochondrial number, structure, or function [272]. The quantity of altered mitochondria changes depending on the type of cancer and their need to grow [273]. Disruption of OxPhos leads to the accumulation of mutagenic and carcinogenic reactive oxygen species (ROS). Cancer cells have higher levels of ROS than healthy cells due to mitochondrial dysfunction [274]. Exogenous ROS sources produce oxidative stress, which leads to mitochondrial dysfunction, resulting in increased endogenous ROS production and potentially tumorigenesis [275]. In the 1920s, Warburg was the first to argue that cancer was initiated by damaged cellular respiration [213,276]. As nuclear mutations occur, mutations in mtDNA are considered secondary risk factors and can only be linked to the origin of cancer if they also disrupt OxPhos function [267]. However, OxPhos is rarely normal in cells containing many mtDNA mutations, which is the case for many cancers [263]. Somatic mutations can only be due to genotoxic carcinogens, limiting the possibility of non-genotoxic agents causing tumors, as explained by SMT. Conversely, OxPhos inhibition or suppression can result from both genotoxic carcinogens [257,277] and non-genotoxic carcinogens [278,279], allowing us to better understand why these two types of compounds can cause cancer. Warburg also noted that acute damage to respiration is more likely to cause cell death [213]. Indeed, a chronic effect of radiation will lead to a decrease in OxPhos activity and ATP production compared to an acute

effect [277]. Although mitochondrial mutation is not essential for tumorigenesis, chronic OxPhos insufficiency appears to be.

4.4. Nuclear Genetic Mutation Versus Mitochondrial Alteration in Tumorigenesis: Experimental Studies

Insufficient OxPhos would be responsible for most of the nuclear genomic changes in cancer, rather than the opposite [214]. Roskelley et al. [280] demonstrated that OxPhos was either defective or insufficient in all cancer cells and that the genome stability depended on OxPhos. Nuclear genomic modifications can occur via three pathways following mitochondrial dysfunction. The first is retrograde (RTG) signaling, which is the specific term for mitochondrial signaling to the nucleus. It involves cellular responses to changes in the state of mitochondria [281]. RTG1 and RTG3 proteins can individually enter the nucleus and modify genome expression [214,282,283]. Chronic mitochondrial stress, also known as mitostress, leads to RTG signals that create instability, overexpression of oncogenes, and inactivation of tumor suppressor genes. The second phenomenon, called numtogenesis, involves the transfer of mtDNA (or less specifically the transfer of mitochondrial components) into the nuclear genome [284]. Mitostress can lead to mitochondrial dysfunction, which in turn can lead to mitochondrial DNA transfer into the nucleus, resulting in genome instability [273,285,286]. The final pathway involves ROS. Bartesaghi et al. [287] have shown that the inhibition of mitochondrial metabolism leads to p53 mutation via a mechanism involving ROS in CSCs. Chandra et al. [288] confirmed that mitochondrial dysfunction induces genetic instability of the nuclear genome. The mechanisms that can generate cancer are summarized in Figure 4.1 below:

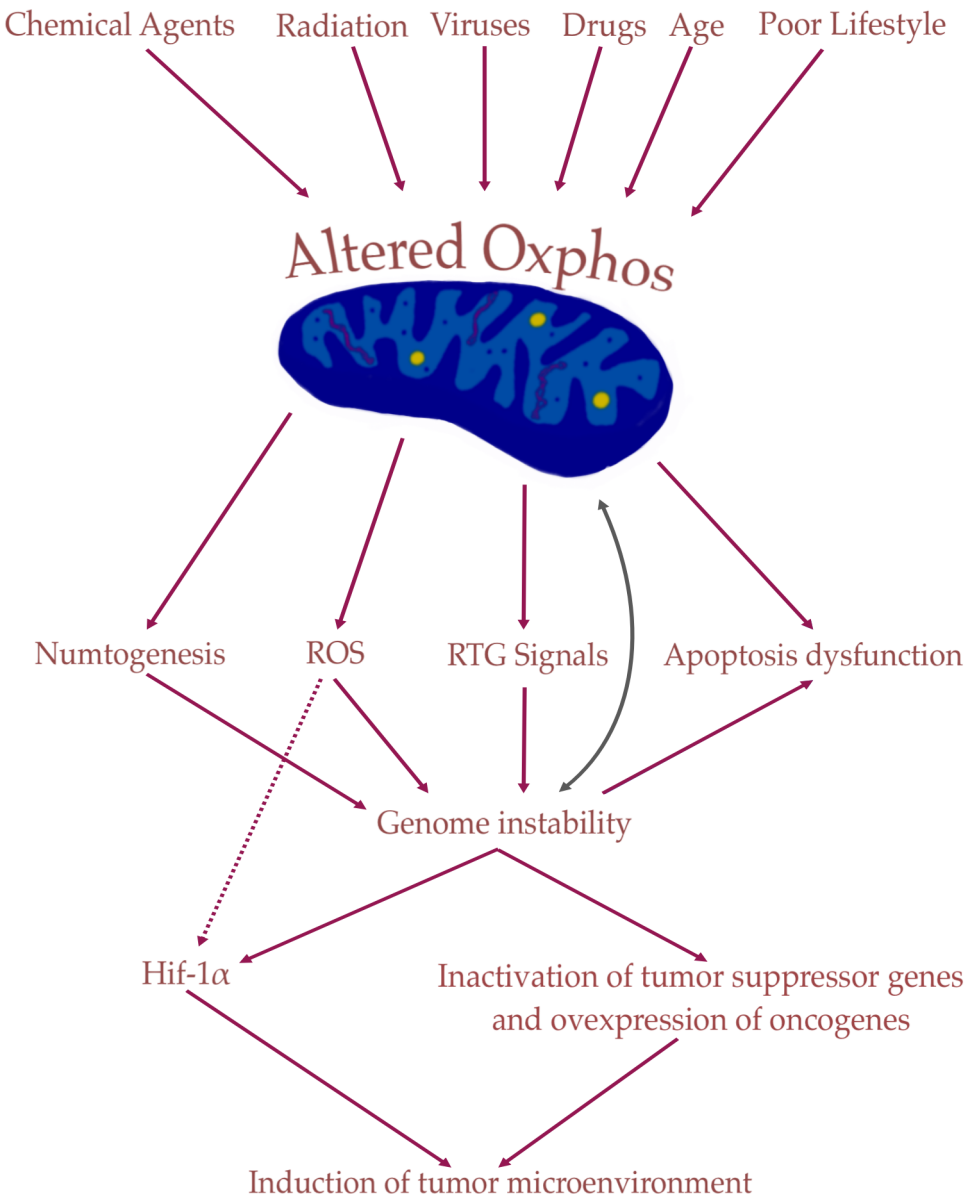

Figure 4.1. Dysfunctional mitochondria drive the alterations seen in the nuclear genome. Insufficient *OxPhos drives alteration of the nuclear genome through three pathways: Numtogenesis, ROS, and RTG Signals. As mitochondria control apoptosis, apoptosis dysfunction would be an expected outcome after insufficient OxPhos. HIF-1α–Hypoxia-Inducible Factor 1α; OxPhos–Oxidative Phosphorylation; ROS–Reactive Oxygen Species; RTG–ReTroGrade.*

RTG signals, numtogenesis, and persistent ROS lead to the expression of numerous oncogenes and the inactivation of tumor suppressor genes, which will allow the development of the tumor environment and abnormal energy metabolism. Chronic mitostress can lead to the alteration of other cellular mitochondria, further reducing cellular respiratory capacity.

Studies both in vitro and in vivo have shown that tumorigenicity is suppressed when the cytoplasm of non-tumorigenic cells (containing normal mitochondria) is combined with tumor cell nuclei [289-297]. Nucleus genetic mutations would not be sufficient, as suggested by repeated cases where cells from various cancer types were normalized when placed in a normal environment [298-300]. Introducing normal mitochondria into highly malignant cells could reverse malignancy and down-regulate several oncogenic pathways. The opposite effect was produced when tumor mitochondria were transferred into the cytoplasm of normal cells [269,301]. These results further suggest that tumorigenesis depends more on mitochondrial dysfunction than on the presence of mutations in the nucleus. In contrast to normal mitochondria's suppressive effects on tumorigenicity, tumorigenicity is enhanced when the nuclei of nontumorigenic cells are combined with tumor cells' cytoplasm or with altered mitochondria [302,303]. All this information is summarized below in Figure 4.2:

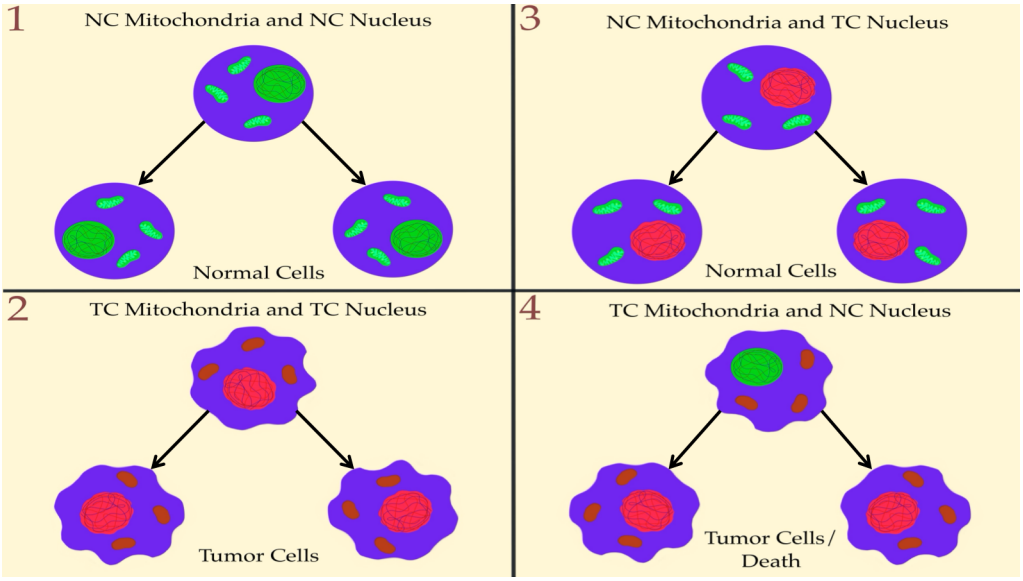

Figure 4.2. Nuclear genetic mutation versus mitochondrial dysfunction. N*ormal cell mitochondria and a normal cell nucleus are depicted in green, with mitochondrial and nuclear morphology indicative of normal respiration and nuclear gene expression, respectively. Tumor cell mitochondria and tumor cell nuclei are depicted in red with abnormal mitochondrial and nuclear morphology indicative of abnormal respiration and genomic instability. **(1)** Normal cell (NC) mitochondria and normal cell (NC) nucleus beget normal cells. **(2)** Tumor cell (TC) mitochondria and tumor cell (TC) nucleus beget tumor cells. **(3)** Delivery of a TC nucleus into an NC cytoplasm (with NC mitochondria) begets normal cells despite the persistence of tumor-associated genomic abnormalities. **(4)** Delivery of an NC nucleus into a TC cytoplasm (with TC*

mitochondria) begets tumor cells or dead cells but not normal cells. This image was extracted and reproduced with a new design with the agreement of Seyfried [214].

These observations are consistent with Darlington's original view that tumor cells arise from defects in the cytoplasm rather than defects in the nucleus [304]. Additionally, recent studies show that the injection of normal mitochondria in tumor cells can negatively regulate several oncogenic pathways and abnormal growth of glioma, melanoma, and metastatic breast cancer cells [301,305-308]. Cuezva and Ristow showed that normal mitochondrial respiration suppresses tumorigenesis [309,310]. Finally, mitochondrial transplantation–in which functional mitochondria are transplanted into cancer cells–could increase cancer cell death exactly like apoptosis. Mitochondrial transfers work differently. They are a natural process of sharing mitochondria between cells, favoring cancer cells. This induces an increase in chemoresistance and the invasive nature of cancer cells that receive the mitochondria of cells from the tumor microenvironment [311].

4.5. Cancer Stem Cells (CSCs) Are Induced by Mitochondrial Damage in Stem Cells: The Origin of Tumorigenesis

CSCs share similar properties with embryonic and adult stem cells: they self-renew in order to maintain the CSCs reservoir, as opposed to non-cancer stem cells (non-CSCs) [312]. They also have the ability of multi-potentiality, which means they can differentiate into all of the cellular components present in the tumor or organ in question, resulting in tumor heterogeneity [312]. Unlike differentiated cancer cells, CSCs are highly tumorigenic [313-315] and can generate a tumor identical to the original one [316]. They have been identified in all different types of cancers [312,317]. CSCs are highly involved in tumorigenesis, metastasis, treatment resistance, and tumor progression [318]. Most, if not all, cancers are believed to arise from a small number of CSCs [319]. The proportion of CSCs in tumor tissues, usually representing only around 2% of the total tumor mass, can vary significantly between different types of cancer [320,321]. Studies have shown that as few as 100 CSCs from the brain, breast, pancreas, lung, and colon can initiate tumors, whereas over 10,000 cells of other non-CSCs cannot do so [322-324]. Injection of 1000 prostate CSCs consistently develops tumors in immunodeficient mice, whereas injection of non-CSCs does not [325]. Mitochondria determine the function of CSCs, including ROS generation, ATP generation by OxPhos, and mitochondrial dynamics. They also determine the fate of these cells, including maintenance, differentiation, survival, proliferation, and resistance. These characteristics (metabolism, oxidative stress, and cell cycle) are altered in CSCs of all types of

cancers [326,327]. CSCs alter their mitochondrial characteristics such as number, morphology, dynamic, associated signaling pathways, and turnover of damaged mitochondria to limit ROS production. CSCs can maintain their reservoir of healthy mitochondria through several processes. First, there is mitochondrial fusion, which consists of the fusion of two mitochondria together, which helps maintain mitochondrial homogeneity, support mitochondrial genome integrity, and maintains the balance between energy production and cell mass. Fusion is generally controlled by proteins (mitofusin 1 and 2 and optical atrophy protein 1). However, the findings connecting mitochondrial fusion with CSCs behavior have not yet been proven [328]. Secondly, mitochondrial fission divides a given mitochondria into two daughter mitochondria. It is achieved by the positive regulation of dynamin-related protein 1, which can be recruited into the mitochondrial membrane from the cytoplasm with the help of mitochondrial receptor proteins (mitochondrial fission 1 protein, mitochondrial dynamics proteins of 49 and 51, mitochondrial fission factor, and dynamin 2). Finally, mitophagy serves to eliminate any damaged or defective mitochondria. Mitophagy is categorized into two subtypes depending upon the protein involved, such as PTEN-induced kinase 1/Parkin-dependent mitophagy and receptor-mediated mitophagy [317]. All of these processes contribute to providing energy for better adaptation of CSCs with stress microenvironment. Age-related deterioration induces ROS accumulation, OxPhos inefficiency, and dysfunction of autophagy/mitophagy mechanisms necessary for maintaining stem cell homeostasis [329], which could increase the risk of cancer with age [329,330]. As previously stated, chemical agents are highly efficient to induce cancer in vivo [221]. In chemically induced cancers, the lesion usually occurs first in the tissue stem cells [331]. Therefore, ROS disrupts mitochondrial homeostasis and OxPhos [256], resulting in the tumorigenicity by CSCs [332]. Consequently, it is suggested that the mitochondrial–stem cell connection (MSCC) highlighted by impaired OxPhos in one or more stem cells could lead to the formation of CSCs and, thus, tumorigenesis. This is shown below in Figure 4.3:

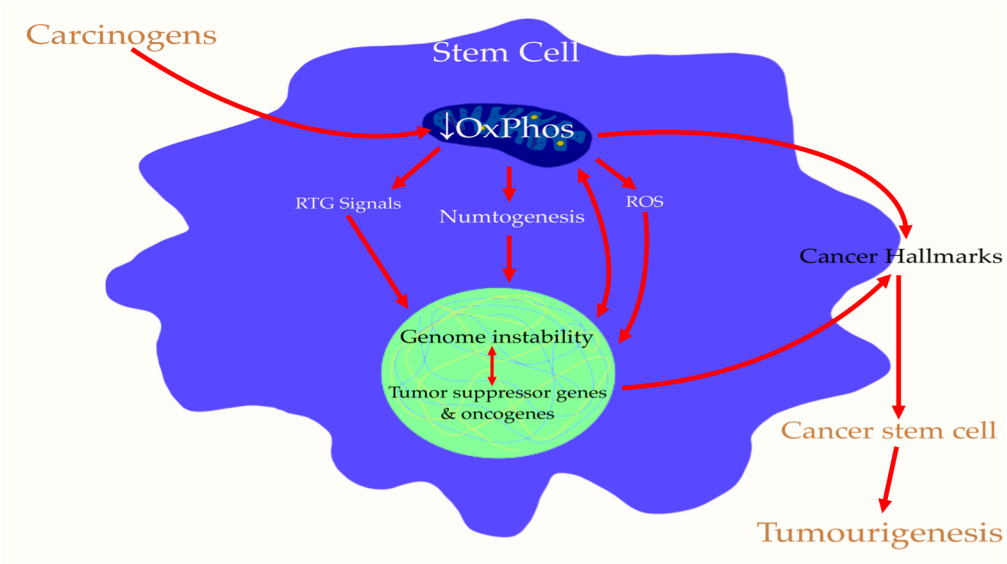

Figure 4.3. The OxPhos alteration in stem cells induces the Cancer Stem Cells. *This figure represents the intracellular mechanisms necessary for the tumorigenesis. OxPhos–Oxidative Phosphorylation; ROS–Reactive Oxygen Species; RTG–ReTroGrade.*

To illustrate the MSCC, a community of dwarfs in Ecuador called Laron dwarfs has a very low incidence of cancer [333,334]. They have a congenital deficiency of Insulin-like Growth Factor one (IGF-1) due to a syndrome called Laron syndrome [335]. Inhibition of IGF-1 receptors has been shown to stimulate pathways that regulate mitochondrial maintenance, including mitophagy [336]. It was demonstrated in dwarf mice with Laron syndrome that they could have a higher number of bone marrow stem cells [337]. Ames dwarf mice generally live longer than other mice, and the lack of growth hormone (GH) secretion results in undetectable levels of plasma IGF-1, just like Laron dwarfs. The consequences of the absence of IGF-1 in those mice are an increase in mitochondrial respiratory activity (OxPhos), a decrease in ROS production, and a mitochondrial DNA/nuclear DNA ratio identical to other mice [338]. In contrast, the upregulation of IGF-1 receptors promotes stem cell tumorigenesis and inflammation [339]. All this seems to confirm the hypothesis of tumorigenesis due to altered OxPhos in one or more stem cells.

4.6. The Metabolism of Cancer Cells Compensates for OxPhos Insufficiency

Cell metabolism is altered in cancer. Cancer cells can find many alternative pathways for their energy needs using glucose, glutamine, lipids, amino acids, and ketone bodies [326,340] and the CSCs have the same energy requirements as non-CSCs [341-343]. Healthy cells produce energy in the form of ATP mainly via two processes, the substrate-level phosphorylation and the OxPhos [344]. Under normal conditions, during the complete oxidation of glucose, 32 ATP

molecules are produced through OxPhos [345]. The best-known effect is the Warburg effect: in all cancers, glucose fermentation enables cell growth since mitochondrial respiration is not sufficient. According to Warburg, glucose fermentation compensates for respiratory failure, and cancer cells continue to ferment whether oxygen is present or not [213,276,346,347]. This phenomenon (Warburg effect) is known as aerobic fermentation. The glycolytic pathway can increase ATP production 100 times faster than OxPhos can [348,349]. On the other hand, the inhibition of glycolysis leads to the death of CSCs [340]. This metabolism allows us to understand the low incidence of cancer in Laron dwarfs. Indeed, the Laron dwarfs have a normal glycemic index, hypoinsulinemia, reduced responses to glucose and insulin, and they have adequate cellular glucose uptake, which all result in the reduced potential development of the Warburg Effect in this population [350]. Another important pathway that compensates for deficiencies in OxPhos is glutaminolysis. The importance of glutamine-driven mitochondrial substrate-level phosphorylation (mSLP) in the glutaminolysis pathway is the second source of ATP for insufficient OxPhos [351]. Glutamine depletion would cause an increase in ROS and lead to a gradual decrease of CSCs [352]. The more malignant a cell becomes the greater the necessity for substrate-level phosphorylation (glycolysis, glutaminolysis) for dysregulated cell growth [353]. Therefore, the degree of malignancy can be linked directly to the energy transition from OxPhos to substrate-level phosphorylation [272]. OxPhos insufficiency leads to the up-regulation of hypoxia-inducible factor 1α (HIF-1α) and c-Myc by oncogenes, increasing glucose and glutamine transporters and thus the glycolysis and glutaminolysis pathways [283,354]. It is also due to these main fuels that it is possible to detect cancers, proving the necessity and ability of tumor cells to capture these fuels. Indeed, radioactive glucose is used as a cancer detection method [355]. Cancer cells take up radioactive glucose, allowing positron emission tomography (PET-Scan) to detect them. The same process is also possible with radioactive glutamine [356]. The glycolysis and glutaminolysis pathways are summarized below in Figure 4.4:

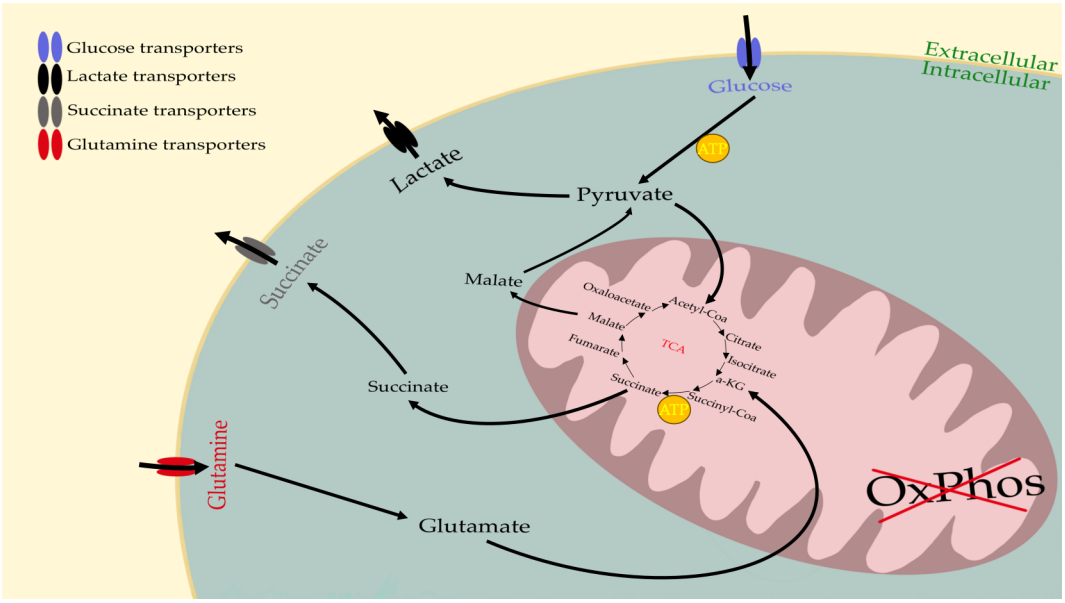

Figure 4.4. The glycolysis and glutaminolysis pathways in cancer cells. *Glucose is taken up into the cytoplasm by specific glucose transporters. α-KG–α-KetoGlutarate; ATP–Adenosine Triphosphate; OxPhos–Oxidative Phosphorylation; TCA–Tricarboxylic/Citric Acid.*

Paradoxically, the energy needs of cancer cells and healthy cells are sensibly identical. The ΔG′ of ATP (standard energy of ATP hydrolysis under physiological conditions) is relatively similar for healthy and cancerous cells. It should be minus 56 kilojoules, meaning that the efficiency of using ATP is similar in cancer cells and normal cells [272]. Indeed, cancer cells are locked into producing ATP through substrate-level phosphorylation, which is insufficient and dependent on an abundant availability of fermentable fuels like glucose and glutamine. To compensate, cancer cells can express the cytoplasmic pyruvate kinase muscle isozyme 1 and 2 (PKM1 and PKM2) isoforms at the last step of glycolysis. PKM1 produces ATP while PKM2 produces little to none [357,358]. Estimating the number of ATP molecules produced by cancer cells can be challenging. Generally, two ATP molecules are produced in the cytoplasm and two others in the mitochondria, but many cancers express the PKM2 and PKM1 isoforms, with only PKM1 generally creating ATP. Consequently, since both PKM isoforms produce lactate but only PKM1 produces ATP, lactate production cannot be used as an accurate marker for ATP synthesis through cytoplasmic glycolysis in tumor cells [358]. Persi et al. [359] showed through their analyses that the high rate of ATP production observed in cancer comes from the cytosol and not from the mitochondria. However, Persi et al. do not take into account the PKM isoforms and the synthesis of ATP by phosphorylation at the mitochondrial substrate induced by glutamine. There is still some confusion regarding CSCs and the use of OxPhos in some studies [328]. First of all, CSCs are known to be able to survive in hypoxic environments and, therefore, in the absence

of OxPhos [360]. Indeed, hypoxia maintains CSCs stemness and promotes resistance through the activation of self-renewal signaling pathways [361]. The confusion may also be largely due to a tool problem. Indeed, the oxygen consumption rate (OCR) is not an accurate surrogate for ATP synthesis through OxPhos in tumor cells. The Seahorse tool is generally used as the primary tool to detect ATP from OxPhos in CSCs [326], but it can only infer that ATP flux is linked to OCR, and it is not yet able to distinguish ATP synthesis from mSLP or OxPhos [272,362]. For these reasons, in cancer cells, OxPhos is neither necessary nor sufficient for tumorigenesis [363] and for cancer progression, as tumor cells can grow in cyanide or in deep hypoxia [364-368]. Pastò et al. [369] also state in their paper that CSCs cannot survive in the absence of pyruvate (the glycolysis end-product) and glutamine. However, it remains unclear whether glycolysis and OxPhos (of healthy mitochondria) can coexist or are mutually exclusive [370]. Thus, as no tumor cells seem to be able to grow and survive in the absence of glucose and glutamine [214,371,372], cancer could correspond more to a metabolic pathology [223]. Glucose and glutamine-driven fermentation by glycolysis and glutaminolysis pathways are cancer cells' metabolic signatures [362].

4.7. CSCs and Macrophages: The Origin of Metastases

CSCs induced by the MSCC are directly involved in metastases. Several authors have reported the presence of CSCs in metastases of different cancer types [373-376]. Unlike their differentiated progeny, CSCs can undergo unlimited self-renewing division [377,378] and, therefore, are able to recreate a distant tumor [379]. For metastases to form, cancer cells must be capable of intravasating into the bloodstream, surviving there, attaching, and recreating a tumor and its microenvironment. CSCs' involvement in the metastatic process seems evident given their adaptive properties [380] partly due to their multipotent capacity [312]. They can initiate a new tumor while conserving the primary tumor's cellular signature [381]. However, CSCs, such as CT-2A and VM-NM1 (murine glioma cell lines), cannot metastasize alone [382]. Another structure seems to have to intervene, namely the macrophages. Macrophages are commonly considered to be one of the key structures in metastases, as they have the capacity to intravasate [383] and may represent up to 50% of the tumor mass [384]. They are generally referred to as "tumor-associated macrophages" [385,386]. A phenomenon called fusion hybridization may involve macrophages to form a hybrid cell necessary for metastases. This fusion can occur with CSCs and/or differentiated macrophages [382]. Moreover, data suggests that macrophages can also allow non-CSCs to reacquire stemness properties [387], a phenomenon known as dedifferentiation [388,389]. However, CSCs may have a higher propensity to fuse with macrophages as their proximity or direct contact with intratumoral macrophages is more frequent than with non-CSCs [387]. Thus,

the systemic metastases can rarely originate directly from CSCs, but most often from fusion hybridization between CSCs and macrophages [382].

4.8. The Tumor Microenvironment of CSCs: A Necessary Consequence of Mitochondrial Impairment

The tumor microenvironment plays a crucial role in the development and growth of tumors, and it is identical for cancer cells and cancer stem cells. Chronic OxPhos insufficiency affects the nucleus, in particular genomic instability. OxPhos insufficiency leads to the up-regulation of HIF-1α and the c-Myc (see Figure 4.1) by oncogenes, increasing glucose and glutamine transporters and thus the glycolysis and glutaminolysis pathways, which allows the development of the tumor microenvironment and their various elements. The tumor microenvironment includes pH, hypoxia, entropy, pressure and deformation, temperature, stroma, cytoplasmic water, and bioelectricity. All of these elements, essential for the maintenance and survival of cancer cells (CSCs and non-CSCs), are presented below:

4.8.1. Pressure and Deformation of Tissues

Paradoxically, tumor tissues are often detected by palpation despite cancer cells being softer than normal cells and cellular stiffness decreasing with cancer progression [390]. The rigidity may not originate from the tumor cells themselves but rather from their microenvironment. Tumors often exhibit high osmotic pressure, which is mainly caused by tumor debris and an increase in extracellular matrix components. This is a consistent characteristic of the tumor microenvironment [391]. The high osmotic pressure in tumors is consistent with the high pressure of the following fluids: interstitial fluid, blood, and lymph [392,393].

4.8.2. pH

One of the consequences of the Warburg Effect is the alteration of cellular pH. Indeed, the Warburg Effect leads to an increase in the absorption of glucose, which will be transformed into pyruvate and then into lactic acid [394]. The expression of PKM1 and PKM2 at the last step of glycolysis, observed in many tumors, contributes to the production of lactic acid [357,395]. The glutaminolysis pathway produces very little lactate [358]. The end-product of the glutaminolysis pathway is succinate (see Figure 4.4), which also contributes to extracellular acidification [396,397]. Furthermore, hyperosmolarity contributes to pH acidification by increasing extracellular Na+ concentration levels, which promotes aerobic glycolysis and leads to lactate accumulation

[391,398,399]. Lactagenesis is a highly orchestrated effort that contributes to glycolysis, glutaminolysis, lactate production, a decrease of mitochondrial functions, angiogenesis, immunosuppression, cell migration, and metastases [396,400,401]. Lactic acid will be evacuated as waste into the extracellular environment, thus decreasing the extracellular pH [402]. In normal cells, the intracellular pH typically ranges from 6.9 to 7.2, while the extracellular pH ranges from 7.2 to 7.4. Nuclear magnetic resonance imaging studies have shown a range between 7.2 and 7.7 of intracellular tumor pH, while the extracellular tumor pH ranges between 6.2 and 6.8 [403-405]. The high production of protons and their migration to the extracellular environment are responsible for establishing this pH gradient in cancer cells [406]. Therefore, the genomic instability and somatic mutations observed in most cancers are a result of the chronic production of ROS (caused by the alteration of OxPhos) and microenvironment acidification [287]. Solid and liquid tumors seem to have the same fuels, glucose, and glutamine [397,407-410], and, therefore, they have the same acidic environment. Indeed, a dependency on glucose and glutamine fermentation leads to the extracellular accumulation of lactic acid and succinic acid, which will acidify the microenvironment, leading to tumor progression.

4.8.3. Hypoxia

Hypoxia is another major component of the tumor environment. Mitochondria-derived ROS can promote cancer initiation through oxidative stress and cancer cell progression via hypoxia-inducing factors, particularly HIF-1α [265]. The activation of RTGs leads to the persistent expression of various oncogenes such as HIF-1α , which induces hypoxia and positively regulates the glycolysis and glutaminolysis pathways (and indirectly the pH) [353]. HIF is also expressed when ROS production increases [411]. Tumor cells are exposed to a continuum of oxygen concentration. The larger the tumor is, the farther some cancer cells will be from the large vessels, resulting in these distant cells being found in a hypoxic environment [412,413]. The more hypoxic a cell is, the less access it has to OxPhos, leading the cell to rely more on substrate-level phosphorylation as an energy source [272],[414]. Hypoxia also contributes to the alteration of anti-tumor immune responses [415].

4.8.4. Entropy

Entropy represents the difficulties of waste evacuation. Cells typically generate heat through the mitochondria and ATP, and this process is disrupted in cancer cells. This leads to increased waste and a disorder called entropy, which is necessary for the cellular heterogeneity of cancer [416]. The loss of energy (ATP) has an immediate influence on the transport of matter

and on the preservation of cellular information, leading to disturbance and, therefore, an increase in entropy [417].

4.8.5. Temperature

One study has shown that the temperature in tumor environments is generally around 1 °C higher than in healthy environments [418]. Moreover, mitochondrial temperature is higher in cancer cells compared to normal cells [419].

4.8.6. Stroma

The stroma includes the extracellular matrix, fibrous proteins such as collagen, growth factors, antibodies, metabolites, mesenchymal support cells, blood vessels, lymphatic vessels, nerves, and immune system cells [420]. In some instances, the alteration in mtDNA can activate mitochondrial retrograde pathways. These pathways lead to epithelial-to-mesenchymal transition-like reprogramming that can promote tumorigenesis and migration. Moreover, mitochondrial RTG signals could regulate Wnt signaling, which can promote tumorigenesis [328]. Stroma has a significant impact on the formation of the tumor microenvironment [421].

4.8.7. Bioelectricity and Cancer

Cancer is characterized by an excessive accumulation of electrons, which reduces the cells' electrical conduction. Higher rates of glycolysis lead to increased electron transfer [422], which is a major contributing factor to the increased production of ROS [423]. In eukaryotic cells, microtubules generating the electromagnetic field comprise tubulin heterodimers with a strong electric dipole. The Warburg Effect in cancer cells results in a reduction in electromagnetic field strength, disrupted coherence, and an increase in oscillation frequency [424]. A comparison of the space between the internal membrane and the mitochondrial matrix of healthy and cancer cells reveals a reduction in the proton gradient, an establishment of the ordered water layer, an increase in electron emissions, and consequently, damping of the electromagnetic field in cancer cells [425]. Behnam et al. [426] suggested targeting the mitochondria with magnetic fields in order to restore the initial mitochondrial magnetic field by reducing the quantity of electrons.

4.8.8. Cytoplasmic Water

In a healthy environment, water molecules carry out three types of motion in space known as vibration, self-rotation, and translation [427]. In cancer, the dynamics of hydration water molecules remain virtually unchanged during the transition from healthy to cancer cells. However, the rotational movements of cytoplasmic water undergo significant changes during

the transition from healthy to cancer cells [428]. Tanner et al. [429] observed alterations and loss of rotation in malignant cells as opposed to healthy cells. It is possible that the rotation of cytoplasmic water molecules is altered due to the loss of the mitochondrial magnetic field.

All of these phenomena are summarized below in Figure 4.5:

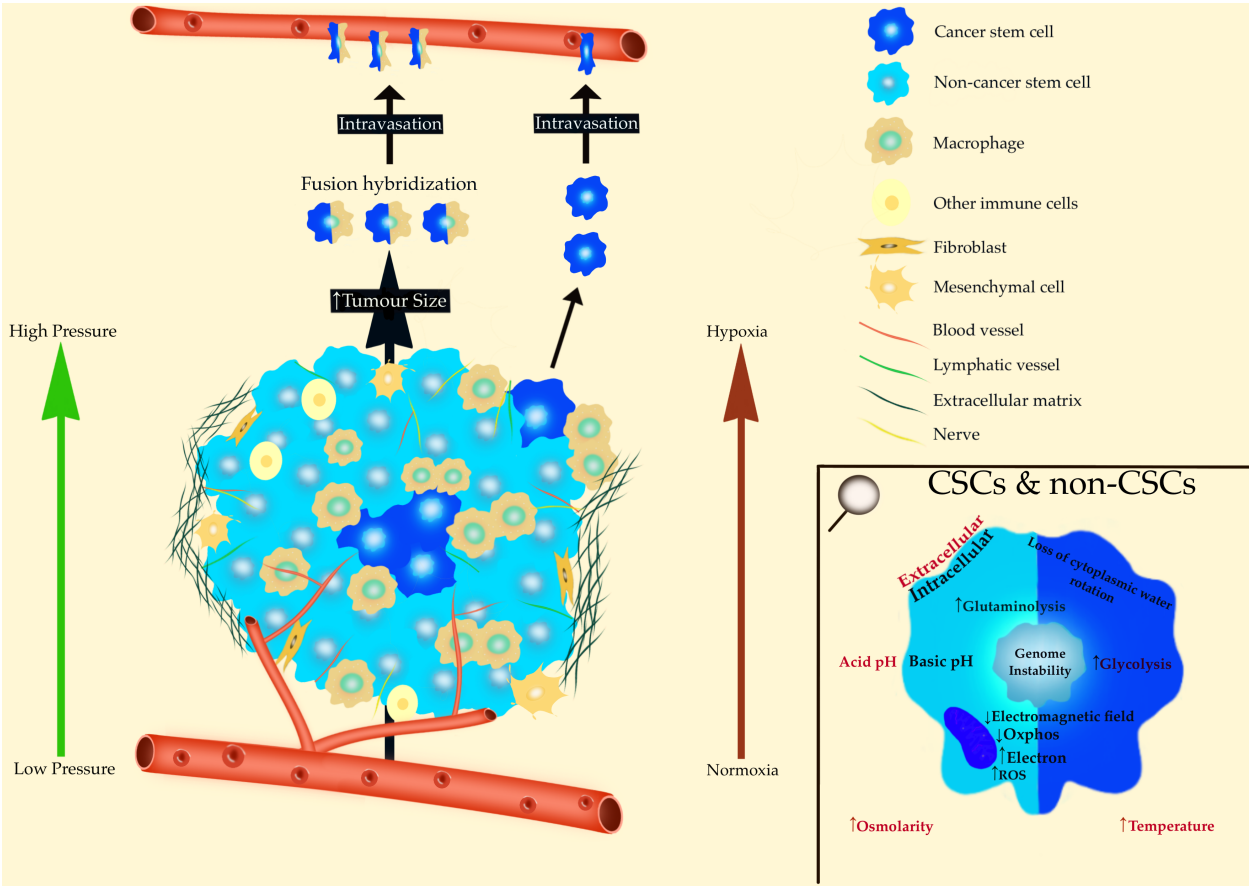

Figure 4.5. The tumor-scale microenvironment is shown on the left. In the enlarged window at the bottom right, the microenvironment is represented at the cellular level. This environment is identical for cancer cells and cancer stem cells. *CSCs–Cancer Stem Cells; non-CSCs–non-Cancer Stem Cells; OxPhos–Oxidative Phosphorylation; ROS–Reactive Oxygen Species.*

The microenvironment has a major role in all stages of cancer, from initiation to metastases [430,431], and mitochondria can regulate and modify the microenvironment [432].

4.9. The CSCs (and Their Mitochondria), an Explanation of the Current Treatments and Relapses

In light of the MSCC, restoring the OxPhos metabolism of CSCs represents a relevant therapeutic lead for potential cancer management [320,433-435], perhaps in combination with

therapies that also target macrophages [436]. Indeed, most current cancer drugs target tumor growth by inhibiting DNA synthesis or cell division of actively dividing cancer cells [437-439], but CSCs are often in a quiescent state [440]. The quiescent state explains the slow growth of cancers [441]. Indeed, chemoradiotherapy targets bulk cancer cells, leading to their death, while CSCs are free to grow and improve their resistance [317,442-445]. CSCs can continue to proliferate as they lack the mutation of the oncogene "targeted" by the drug and, therefore, do not respond to treatment [446,447]. This may explain the slight improvement with new therapies. Ladanie et al. showed that over the past fifteen years, the improvement in overall survival by new therapies is 2.4 months [448]. Another study reports an improvement of 3.4 months over the last thirty years [449]. Additionally, current therapies do not restore OxPhos and can sometimes alter it [255,434,450-453]. The lack of OxPhos restoration allows a better understanding of why many patients only have a partial response and end up relapsing, showing a tumor that is often more resistant and more conducive to the formation of metastases [454,455]. Indeed, chemoradiotherapy can induce prometastatic niches in other organs [456], in which macrophages will then frequently fuse with CSCs to reinforce resistance to treatments [385]. Moreover, the majority of detected cancers are non-metastatic and typically require surgery in combination with standard multitherapy [457]. A significant proportion of healing can be attributed to the combination of existing treatments that target the bulk of cancer cells [442] and surgeries that remove CSCs through excision. Indeed, melanomas, thyroid cancers, kidney cancers, prostate cancers, uterine corpus cancers, testicular cancers, and breast cancers are excellent examples of the effectiveness of surgery on non-metastatic cancers [92]. Another example is pancreatic cancer, which has the lowest survival rate among all cancers. When the tumor is resectable (rare), excision is the only possible cure for this cancer [458]. The primary challenge in cancer treatment remains metastases [459], which account for approximately 90% of cancer deaths [459] and are rarely operable [92]. Standard therapies do not eliminate CSCs (and their mitochondria) [442,450,451,460], which, associated with macrophages, can form metastases [382]. The relapse phenomenon follows the same logic. Considering that CSCs cannot be targeted and represent ≈ 2% of the total tumor mass [320,321,461,462], the vast majority of tumor-forming cells (bulk cancer cells, macrophages, etc.) can die after conventional therapies [442,463,464], allowing the reduction or even temporary disappearance of the tumor [465]. Yet, the new PET-Scan models have a detection limit of 4 mm [466], knowing that a 5 mm cancer has approximately 10 million cells and a 1 mm cancer has approximately 100,000 cells [467]. Since the lower detection limit of a PET-Scan is around 10^5 to 10^6 malignant cells [468], CSCs can fall below the PET-Scan detection threshold, giving the impression of remission before reappearing a few months or years later. Many agents can target the pathways that are associated with CSCs,

such as Vismodegib, Glasdegib, MK-0752, OMP-54F28, and Selinexor [469]. However, these agents do not specifically target the mitochondria and, more particularly, do not induce the restoration of OxPhos. Many other therapeutic strategies have been proposed to target mitochondria, such as Resveratrol, Metformin, and Melatonin. These can target the mitochondrial dynamics or OxPhos [470]. For example, drugs such as Metformin or Phenformin can alter OxPhos by electron transport chain (ETC) inhibitors. Antibiotics such as Doxycycline, Tigecycline, and Bedaquiline can target mitochondrial biogenesis. The drug Mdivi-1 targets mitochondrial dynamics, while 188Re-liposome and the inhibitor liensinine block the mitophagy [326,328]. Most of the time, these treatments do not restore mitochondrial homeostasis [341], but mainly restore or alter only a few parts of the dysfunction. This seems to be insufficient. In addition, therapies that might involve targeting mitochondria in tumor cells have to be used cautiously. Mitochondrial targeting can have lethal off-target effects on OxPhos metabolism in normal host cells. These toxic effects include nausea, seizures, and even coma [471,472]. Therapies aimed at increasing OxPhos, such as hyperbaric oxygen therapy, could be relevant. This would increase the activity of OxPhos and would have tumor suppressor effects [473]. A ketogenic diet or fasting could inhibit the fuels necessary for cancer cells while increasing the activity of OxPhos as well [474].

4.10. Key Points of the MSCC

Chronic insufficiency of OxPhos in a stem cell may be a keystone of cancer and its different steps, according to MSCC. The approach provided by the MSCC is summarized in Figure 4.6.

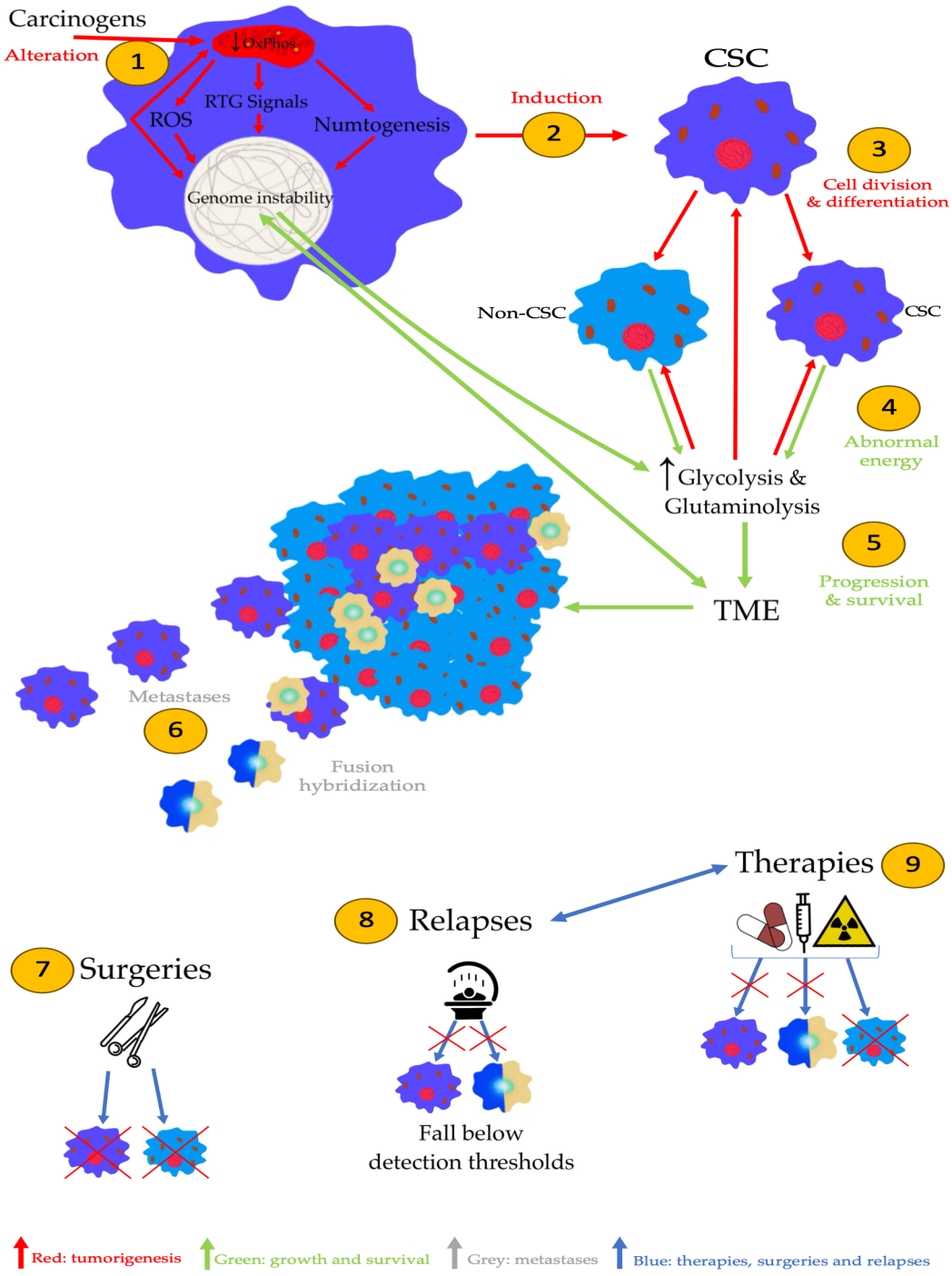

Figure 4.6. Synthesis of MSCC. *(1) Carcinogens alter OxPhos in stem cell(s). (2) OxPhos alteration in stem cells induces cancer stem cells (CSCs). (3) CSCs can be divided into other CSCs or non-cancer stem cells (non-CSCs). (4) Metabolism of cancer cells compensates for OxPhos insufficiency with glycolysis and glutaminolysis. The chronic ROS, the RTG signals, and the numtogenesis induce overexpression of oncogenes and inactivation of tumor-suppressor genes, which contribute to abnormal energy metabolism in cancer. (5) The abnormal metabolism and oncogenes contribute to generating the tumor microenvironment (TME). The acidification, inflammation, and chronic production of ROS contribute to genome instability*

and somatic mutations. (6) Metastases are produced by CSCs directly (rare) or by fusion hybridization with macrophages. (7) Local surgeries in non-metastatic cancers can target non-CSCs and CSCs. (8) CSCs and their fusion hybridizations with macrophages are present in low numbers and can fall below detection thresholds. (9) Therapies can target only non-CSCs. CSCs–Cancer Stem Cells; non-CSCs–non-Cancer Stem Cells; OxPhos–Oxidative Phosphorylation; ROS–Reactive Oxygen Species; RTG–ReTroGrade; TME–Tumor Microenvironment.

(1) Tumorigenesis: OxPhos alteration in one or more stem cells (MSCC) creates the CSCs, which could lead to tumorigenesis.

(2) Growth and survival: OxPhos insufficiency induces genomic instability and alters the expression of oncogenes and tumor-suppressor genes, which can contribute to the tumor microenvironment and abnormal energy metabolism required for tumor survival and progression. Cancer cells (CSCs and non-CSCs) depend critically on fermentable fuels, namely glucose and glutamine.

(3) Metastases: The metastases can rarely originate from either CSCs (induced by MSCC) directly but more frequently from fusion hybridization between CSCs and macrophages. The tumor progression and malignancy can be directly linked to the energy transition from OxPhos to substrate-level phosphorylation (glycolysis, glutaminolysis). Thus, the higher the degree of mitochondrial abnormalities (decrease in OxPhos), the greater the degree of malignancy.

(4) Healings, failures, and relapses: Curing cases can be explained by the capacity of standard care to target the CSCs, while treatment failures may be attributed to their inability to do so. Relapses may occur due to the low number of CSCs (alone or fused with macrophages), which could fall below detection thresholds despite their presence.

4.11. Conclusions

According to the MSCC approach, tumorigenesis could result from a mitochondrial alteration (metabolic model) in one or several stem cells (CSCs models) forming the CSCs. Genomic instability and somatic mutations are effects of insufficient OxPhos leading to abnormal energy metabolism and a tumor microenvironment (TOFT), contributing to cancer cell progression and survival. The reviewed information shows that the respiratory impairment of stem cells could be one keystone of cancer and is necessary for all the different steps, from tumorigenesis to metastases. The metabolism also plays a significant role in cancer, since the tumor must compensate for the altered OxPhos, mostly through glycolysis and glutaminolysis.

This MSCC approach opens up many therapeutic leads for cancer management. The first would involve the simultaneous restricting of glucose and glutamine availability while transitioning the body to non-fermentable fuels like ketone bodies and fatty acids. The second approach would be specifically restoring cellular respiration (OxPhos) in CSCs. An important goal in preclinical models and human cancer patients will be to demonstrate that the restoration of OxPhos, combined with simultaneous targeting of glucose and glutamine while under therapeutic ketosis, should permit the elimination of CSCs and thus reduce tumorigenesis and metastases. The tumor microenvironment described in this chapter – characterized by hypoxia, acidosis, pressure, entropy, temperature, and immune dysregulation – is precisely the environment that drives the chronic overstimulation of vagal afferent fibers and the progressive inhibition of vagal efferent activity documented in Chapter 6. The MSCC framework thus provides the pathophysiological substrate for understanding why CVT is systematically low in cancer patients: it is not an epiphenomenon, but a mechanistic consequence of mitochondrial impairment at the system level.

Understanding that tumor progression is rooted in mitochondrial dysfunction and sustained metabolic stress helps explain why the autonomic nervous system – and vagal efferent activity in particular – is chronically impaired in cancer. The logical therapeutic response is to identify the most potent, trainable, and non-invasive means of restoring CVT. Chapter 5 examines the neuroscience of breath-hold diving, which, to our knowledge, produces the strongest and most reproducible vagal stimulation documented in healthy humans.

5. Chapter 5: Physiological basis of cardiac vagal tone in breath-hold diving.

This Chapter is essentially drawn from:

Martinez P, Dutschmann M, Epercieux V, Gourjon G, Joulia F. Breath-hold diving as a tool to harness a beneficial increase in cardiac vagal tone. Respir Physiol Neurobiol. 2025 May-Jun;334:104416. doi: 10.1016/j.resp.2025.104416.

General abstract and Key Points of the Article :

This article is the result of more than 2.5 years of work. At the crossroads of basic research and clinical research, it updates the knowledge gained and clinical observations on the fundamental physiological principles of breath-hold diving. We attempted to explain the underlying mechanisms of this discipline and the mechanisms that generate CVT. Indeed, after observing that breath-hold diving is a unique discipline regarding the stimulation of CVT, we found that:

- CVT during breath-hold is generated in the brainstem by the association of two key nuclei: the Kolliker-Fuse and the pre-Bötzinger Complex,
- The Kolliker-Fuse stimulates the cardiac vagal motoneurons from the nucleus Ambiguus (nA) and leads to bradycardia or increased HRV,
- The additional and synergistic mechanisms of breath-hold depend on the type of breath-hold practiced,
- One of the most powerful additional mechanisms is nasal immersion in cold water, which leads to stimulation of the trigeminal nerve followed by the vagus nerve via the Kolliker-Fuse,
- Breath-hold related neurons exhibit neural plasticity and memory through glutamatergic receptors,
- Thus, breath-hold is a discipline that could be useful for inflammatory and sympathetic pathologies.

This article has enabled the acquisition of the complex physiological foundations underlying breath-hold, and thus a better understanding of the neurons that could be responsible for CVT. It has also helped identify the additional and synergistic physiological mechanisms that could be combined for more powerful CVT stimulation.

5.1 Introduction

The autonomic nervous system is generally seen to regulate involuntary physiologic processes including breathing, heart rate, blood pressure, digestion, and sexual arousal. The interaction between the sympathetic and parasympathetic nervous systems can be both synchronous and synergistic under certain physiological and pathophysiological conditions (for review see [475]). Medical assessment of general health and the status of autonomic nervous system employs the analysis of HRV, which displays indicators of both sympathetic and parasympathetic tone [11,476]. In particular CVT has been identified as a major indicator of general health [477] and low levels of CVT show high correlation with mortality [15]. Therefore, non-invasive or behavioral health interventions that increase CVT could provide major health benefits. However, slowing of the heart rate and consequently an increase in CVT is difficult to achieve without pharmacologic therapies and only specific practices that stimulate a vagal response of the heart, like deep breathing, meditation or yoga provide a degree of "volitional control" of CVT. Unfortunately breathing related practice of meditation and yoga often require years of training and are often burdened by cultural prejudice and therefore additional avenues to effectively increase CVT are urgently required.

The most powerful vagally mediated bradycardia is seen during the mediation of upper airway reflexes that protect the lungs from invasion of foreign or harmful substances [478-481]. These reflexes cause immediate glottal closure and are evoked by mechanical stimulation of either the laryngeal or the nasal mucosa [479]. The latter is commonly referred to as the diving response in mammals and is most pronounced in animals with aquatic or semi-aquatic lifestyles [480]. Based on reports that aquatic mammalian species can initiate an anticipatory bradycardia seconds before a breath-hold dive [482,483] we explore the possibility to use neuroanatomical pathways linked to mediation of the diving response (for review see [480,481]) to influence and improve CVT with regular breath-hold dive (BH-D) exercises. In the following paragraphs we provide a scientific framework that illustrates that BH-D can selectively modulate the brainstem networks that generate respiratory heart rate variability via a mechanism of synaptic plasticity and learning and memory link to volitional breath-hold in association with nasotrigeminal stimulation during face immersion.

5.2 The central mediation of respiratory Heart Rate Variability (respirHRV)

Heart rate is never constant and displays a physiological variability which is closely associated with breathing. We prefer to use the term respiratory heart rate variability (respirHRV) rather than the commonly used term respiratory sinus arrhythmia (RSA), which may have a negative or pathological connotation [484]. RespirHRV is generated by the interplay of synaptic activities in cardio-respiratory control networks in the brainstem [485-487] causing an transient increase in HR during inspiration and a decrease in HR during the early phase of expiration, which is also called postinspiration [488]. The increase in HR during inspiration was previously attributed to an increase in cardiac sympathetic drive during inspiration. However, the conduction velocity of unmyelinated sympathetic fibers is too slow to mediate the increase in heart rate during inspiration [489,490]. Thus, respirHRV is considered to be solely caused by respiratory related fluctuation of CVT.

According to the current understanding of respiratory pattern generation a 3 phase respiratory motor pattern of inspiration, postinspiration (early expiration) and expiration (late expiration) is generated via specific excitatory and inhibitory synaptic interaction of subsets of respiratory neurons [491-494] (Fig. 5.1). In parallel subsets of these respiratory network neurons also modulate cardiac vagal motoneurons (CVMNs) located in the nA to generate respirHRV [495-501]. CVMNs of the nA are the primary source of CVT and myelinated B fibers, which mediate the vagal bradycardia [502-513]. Contrary neurons of the dorsal motor nucleus of vagus nerve, have reportedly no role [502], or only contribute marginally to mediating bradycardia [507,509,514,515].

The anatomical framework for respirHRV is the innervation of the nA from the pontine respiratory group (PRG) [516,517] and the ventral respiratory column (VRC) [518,519] of the medulla oblongata (Fig. 5.1). Research studies further identified that synaptic interactions between the Kölliker-Fuse nucleus (KF) in the pons and the pre-Bötzinger complex (pre-BötC) in the medulla oblongata may play the leading role in respirHRV generation [499,501].

In brief, during inspiration, the pre-BötC neurons provide synaptic drive for phrenic pre-motor neurons of the VRC. However, subsets of inhibitory (glycinergic) inspiratory neurons of the pre-BötC suppress the activity of vagal cardiac preganglionic neurons of the nA (Fig 5.1A). Consequently, the decrease in cardiac vagal drive results in net increase in heart rate during the inspiratory phase of the respiratory cycle [501,520]. After the KF mediated phase transition from inspiration to postinspiration [521,522] the distinctive decrease in heart rate during expiration is most likely mediated by two mechanisms: (i) the withdrawal of synaptic inhibition arising from

the inhibitory inspiratory pre-BötC neurons and (ii) descending excitatory drive to cardiac vagal motor neurons arising from the KF (Fig. 5.1B).

In summary, respirHRV is thought to be mainly generated by alternating activity of pre-BötC and the KF respiratory neurons on cardiac vagal preganglionic neurons during inspiration and postinspiration. Conceptually important for this review is that neurons that innervate CVMNs co-innervate inspiratory and expiratory (postinspiratory) laryngeal motor neurons (see Fig. 5.1). This specific connectivity CMNs and laryngeal motor neurons is the anatomical source that allows for harnessing CVT via volitional breath-holding during free diving exercises (details see below).

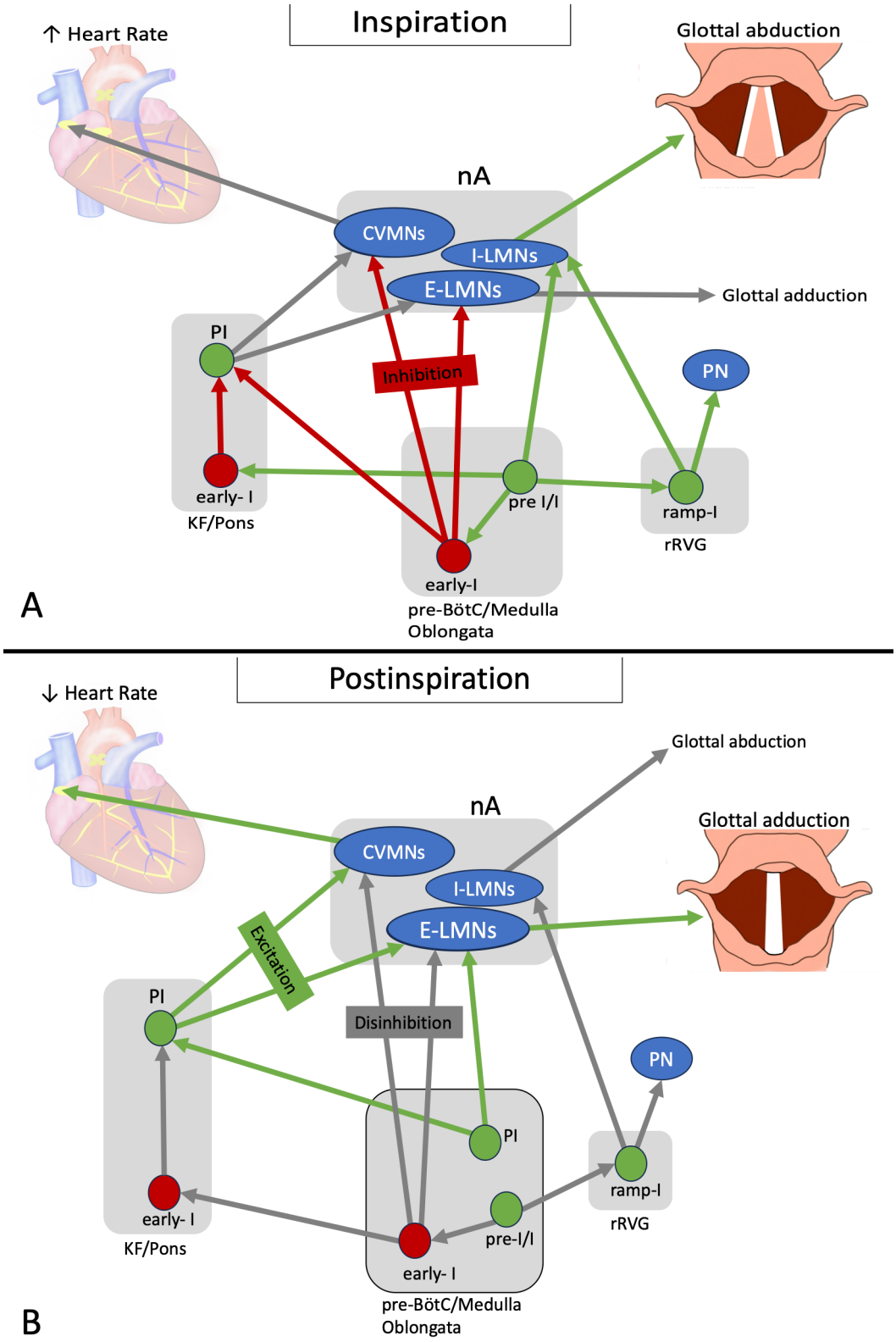

Figure 5.1. Simplified representation of excitatory and inhibitory synaptic neurons involved in the simultaneous generation of the respiratory motor pattern and respiratory sinus arrhythmia of the heart.

*Excitatory neurons are highlighted in green, inhibitory neurons in red and inactive cell populations in gray. For simplification we only refer to two respiratory nuclei that have key roles in the generation and gating of the inspiratory and postinspiratory motor activities: the Kölliker-Fuse nucleus (KF) of the pons and pre-Bötzinger complex (pre-BötC) of the medulla oblongata. While the synaptic mechanisms underlying respiratory rhythm generation involve a variety of additional mechanism, neuron types and brainstem areas [491,523-525], the figure is simplified to focus on four most relevant neuron types: pre-inspiratory/inspiratory (pre-I/I) respiratory rhythm generating neurons; ramp inspiratory (ramp-I) premotor neurons, early inspiratory interneurons and postinspiratory premotor and interneurons (PI). Importantly subsets of neurons innervate inspiratory and expiratory laryngeal motor neurons (I-LMNS, E-LMNS) of the nucleus of ambiguus (nA), the phenic motor neurons of spinal cord (PM) and importantly also connect to the cardiac vagal motor neurons (CVMNs) of the nA to influence heart rate. (**A**) Illustration of the activity pattern and configuration of the brainstem network during inspiration. Please note that according to our current knowledge glycinergic inhibitory early-inspiratory neurons of the Pre-BötC project directly to the cardiac vagal motor neurons (CVMNs) and provide synaptic inhibition during inspiration [501], consequently causing the respirHRV-specific increase in heart rate. In parallel early-I neurons inhibit medullary and pontine postinspiratory PI-neurons [521] and the E-LMNs [526]. (**B**) Same schematic representation of the activity pattern that causes the postinspiratory laryngeal adduction during the early phase of expiration (for physiological significance see text) and the disinhibition (withdrawal of inhibition originating from early -I neurons) and excitation (KF pathway) of CVMNs that cause the respirHRV specific decrease in the heart rate during early expiration. In addition, the KF receives ascending excitatory glutamatergic inputs from pre-BötC neurons [518,519,527] and the same neurons likely also connect to E-LMNs to mediate postinspiratory respiratory motor output [528]. In summary the depicted anatomical connectivity of CVMNs and E-LMNs of the nA with respiratory network neurons suggests that parallel pathways can simultaneously mediate glottal adduction and increase in cardiac vagal tone during postinspiration. The latter provides the critical framework for the proposed mechanism that modulates cardiac vagal tone during volitional breath-hold during diving.*

5.3 Control of cardiac vagal motor neurons during reflexes and volitional breath-hold.

The CVMNs located in the nA are also specifically activated during a wide range of reflexes that trigger reflex bradycardia including the occulocardiac reflex, the Hering-Breuer reflex of the pulmonary stretch receptors as well as arterial baro- and chemoreceptor reflexes [475]. CVMNs are also activated during nociception and during certain defense behaviors [475]. Nevertheless, the most pronounced reflex bradycardia can be evoked by irrigation of the nasal or laryngeal mucosa with water or stimulation with noxious substances and gases [529,530]. These protective upper airway reflexes are referred to as the laryngeal adductor reflex [488] or the nasotrigeminal (diving) reflex [479,531]. Both reflexes elicit laryngeal adduction and consequently glottal closure (breath-hold) to protect the lower airways from the invasion of potentially noxious substances.

In CNS laryngeal adduction is mediated by tonic activation of both inhibitory and excitatory postinspiratory pre-motor neurons of the respiratory network [479,532-534]. These neurons either provide excitatory drive for the expiratory (postinspiratory) laryngeal motor neurons of the nA [535] or inhibit neuron of the respiratory network to terminate inspiration [491]. As described above the inhibition of inspiratory neurons will also cause the disinhibition cardiac vagal motor neurons and thus is a key priming mechanism for the gating of either laryngeal or nasotrigeminal evoked reflex bradycardia. The reflex bradycardia is an oxygen conserving mechanism for circumstances when inspiration and thus oxygen uptake needs to be suspended to protect the lungs from potentially fatal injury [536]. Here, the reduction of cardiac activity, which is a major source of oxygen consumption, is seen as a key mechanism of oxygen conservation [536].

Breath-holding is also a volitionally controlled respiratory behavior and thus may represent a mechanism to actively modulate CVT, which is otherwise not consciously accessible. Previous anatomical tract tracing studies [518,527,537] identified monosynaptic descending projection neurons in the medial prefrontal cortex (infralimbic, prelimbic), somatosensory, insular, motor cortex and claustrum that specifically target the KF and pre-BötC (See Fig 5.2). Most of the aforementioned forebrain structures are also reported to be involved in volitional breath hold in humans [538,539] supporting validity of these descending cortico-bulbar projections for human medicine.

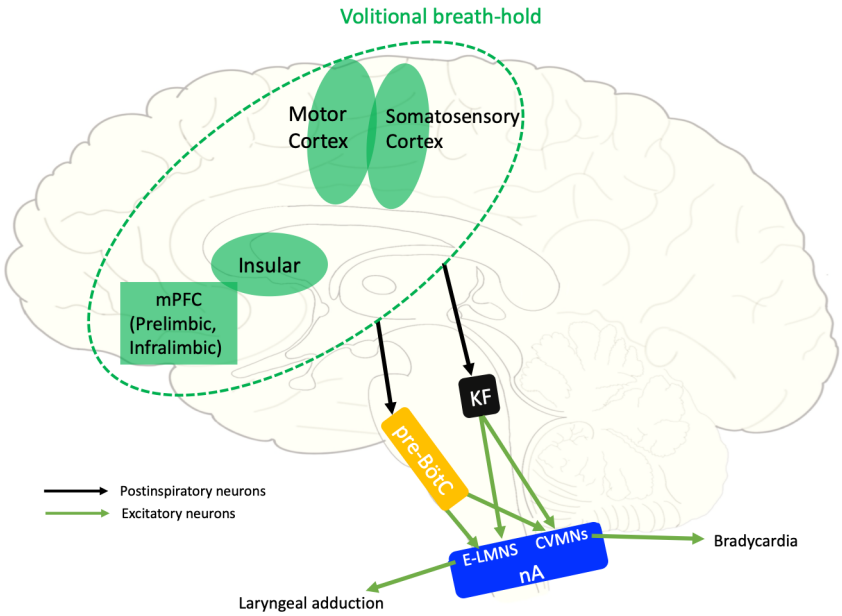

Figure 5.2. Indirect control of cardiac vagal tone via volitional breath-hold. *Descending forebrain projections (black arrows) that target the laryngeal adductor pre-moto population of the KF and pre-Bötz to mediate breath-hold and to target CVMNs in parallel to modulate cardiac vagal tone. This anatomical framework provides support of our working hypothesis that cardiac vagal tone can be indirectly modulated by voluntary breathing exercises, particularly including breath-hold. CVMNs: Cardiac Vagal Motoneurons; KF: Kölliker-Fuse; mPFC: medial Pre-frontal Cortex; nA: nucleus Ambiguus; E-LMNs: Expiratory Laryngeal Motoneurons; pre-BötC : pre-Bötzinger Complex.*

Of particular interest is a case study that implemented functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG) during a static dry volitional breath-holding performed by professional free diver. The study identified similar cortical regions (precuneus, frontal cortex, and occipital cortex) [538] as seen in similar studies using volitional breath-hold to study brain activation mapping in health subjects without diving experience [539]. The key difference between volitional breath-holding in normal subjects and elite divers is the occurrence of robust bradycardia during dry static breath-hold which is absent in non-divers [540]. Volitional breath-hold alone does not necessarily trigger a bradycardia (this may be different for elite divers), but if combined with nasotrigeminal sensory stimulation during irrigation of the nasal mucosa it can reliably trigger bradycardia [541,542]. Indeed, the drop in heart rate can generally greater in non-elite divers when there is an irrigation of the mucosa with cold water [543] compared to a volitional dry breath-hold [540]. In other words, CVT cannot be influenced volitionally, but it can be gated by nasotrigeminal sensory inputs associated with face

immersion during volitional breath-holding during diving. In the following chapter we further explore the unique features of BH-D that allow humans to increase overall CVT and how diving can promote brain plasticity to increase in vagal tone via simple volitional exercises.

5.4 Converging multi-modal sensory and cardiac vagal motor pathways in the brainstem gate the diving bradycardia.

The nasotrigeminal reflex or diving reflex is initiated after irrigation of the nasal mucosa which is innervated by the ethmoidal nerve (EN5) a branch of the ophthalmic division of the trigeminal nerve (V1). Either stimulation of the nasal mucosa with fluids [478,529] or noxious gases (e.g. ammonia vapor), [478,530,532,544] or electrical stimulation of the ethmoidal nerve evokes the nasotrigeminal reflex consisting of breath-hold (apnea), bradycardia and peripheral vasoconstriction (Dutschmann and Herbert, 1996; 1998; Dutschmann and Paton, 2002a). The EN5 also mediates sneeze [545-547] and thus is seen as the first line of upper airway defense that either clears the upper airway of potentially harmfully substances (sneeze) or prevents the invasion of noxious substances into the lungs (breath-hold) [480]. The EN5 contains approximately 65% of non-myelinated C fibers, with a smaller portion consisting of small-diameter Aδ fibers, which are involved in the mediation of nasal nociceptor and mechanoreceptor inputs [548]. Consequently sectioning the EN5 eliminates both the nasotrigeminal reflex [549] and sneeze reflex [550]. The sensory inputs of the EN5 are centrally relayed via pars caudalis of the spinal trigeminal nucleus (Sp5C)[480,530,544,551], see Fig. 5.3a.

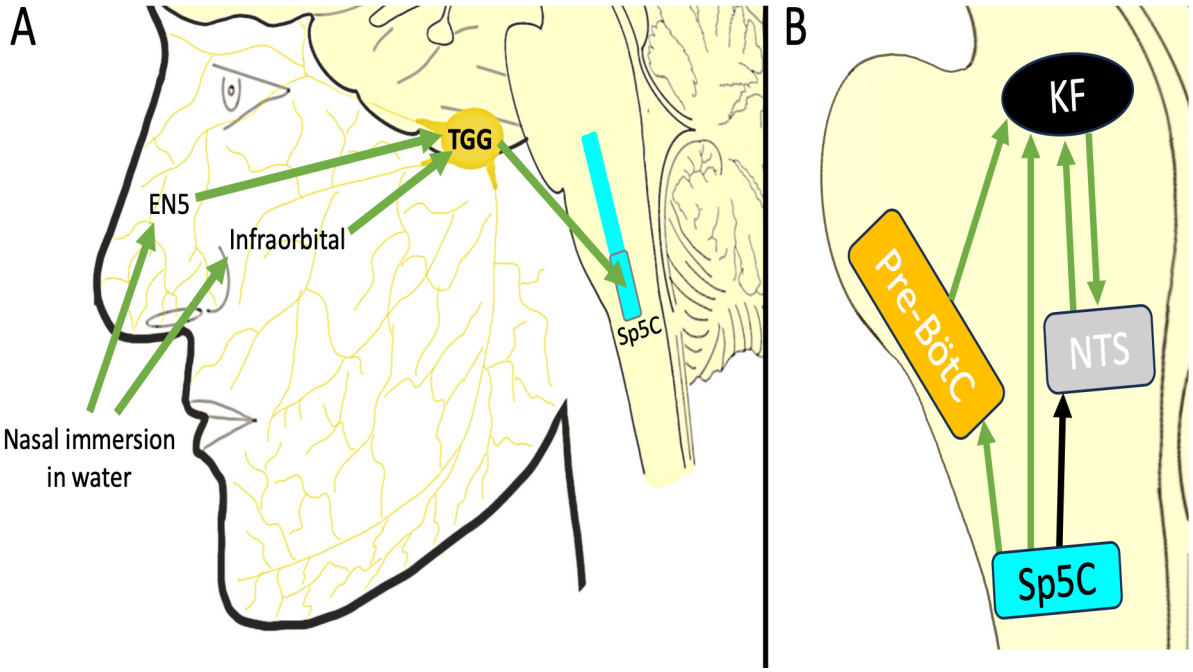

Figure 5.3. Schematic illustration of sensory inputs and central pathways that mediate the nasotrigeminal (diving) reflex. *Excitatory neurons are highlighted in green and neuron projection in black. (**A**) illustrates the key trigeminal sensory inputs arising from the ethmoidal nerve (EN5) and infraorbital nerve that are activated during face immersion and trigger the nasotrigeminal reflex. The trigeminal chemo and mechanoreceptors that sense water in the nose and around the forehead are projecting via the trigeminal ganglion (TGG) to spinal trigeminal nucleus pars caudalis (Sp5C). (**B**) illustrates the projection of Sp5C sensory relay neurons with the brainstem. Please note that these projection neurons target the pre-Bötzinger Complex* [481,552]*, the Kölliker-Fuse (KF)* [553,554]*, and thus the core network for the generation of respirHRV. Additional brainstem projections target the nucleus tractus solitarii (NTS)*[551,555].

Please note that BH-D is associated with face immersion and thus additional trigeminal sensory inputs form the forehead (frontal nerve and supra-orbital nerve, V1 branch) and the paranasal and orbital skin (infraorbital nerve, a branch of maxillary division of trigeminal nerve) areas of the head are also activated. All these afferent sensory inputs are relayed within the Sp5C [480,556]. The functional anatomy of the sensory-motor network of the nasotrigeminal reflex beyond the Sp5C was further elucidated by using the c-fos method which allow for the mapping of the location of nasotrigeminally activated neurons in the brainstem [480,529,555,557]. These studies have identified the location of sensory relay neurons in the Sp5C and illustrate the involvement of neurons in variety of cardio-respiratory control areas of the brainstem including the caudal pressor area, the subnuclei of the NTS, the raphe pallidus nucleus, the rostroventrolateral

medulla, the A5 area, the locus coeruleus nucleus, the pontine KF area, pre-BötC and the parabrachial nucleus. The key pathways involved in the central mediation of the protective breath-hold and diving bradycardia are summarized in Fig 5.3.B. Electrophysiological recordings provide evidence that EN5-evoked breath-hold is associated with tonic drive of postinspiratory medullary neurons [479,545]. The postinspiratory premotor neurons of the KF [558,559] like control the nA expiratory motoneurons that mediate glottal constriction during diving and other respiratory related behaviors [488,560]. As discussed before synaptic drive arising from postinspiratory neurons is also involved in the mediation of respirHRV and also play a key role in the synaptic gating of the diving bradycardia. The tight coupling of glottal adduction and bradycardia during nasotrigeminal stimulation is illustrated in Figure. 4 of Dutschmann and Paton, 2002a. The latter support the hypothesis that during diving synaptic interactions underlying the mediation of the respirHRV (see Fig. 5.2) are utilized to gate the diving bradycardia.

Amongst the brainstem areas in volved in the mediation of the nasotrigeminal reflex experimental evidence suggests that pontine KF subserves a key role in mediation of the diving bradycardia and protective breath-hold. (i) The KF is a primary target of pronounce ascending projections arising from the Sp5C [553,554] that receive sensory input from the head and particular the nasal mucosa [555]. (ii) Pharmacological manipulation of the KF can either augment or attenuate the breath-hold [531,561]. (iii) The KF has a identified role in the mediation of CVT and particular the respirHRV [499]. (iv) The KF receives monosynaptic inputs descending from the cortex that could mediate volitional breath-hold [537,562]. Nevertheless, experiments show that the nasotrigeminal reflex can still persist after ponto-medullary transection [563] suggesting a strong redundance within brainstem circuits for this life-saving and oxygen conserving reflex. In the medulla research show that the pre-BötC has a similar connectivity with Sp5C [481,564], also has role in the gating of postinspiratory (laryngeal adductor) motor activity [528] and respirHRV [501] and as well receives descending synaptic inputs from the forebrain [537] that could mediate volitional breath-hold. The generation of postinspiratory motor activity linked to glottal constriction during breathing and glottal closure during diving engages a vastly distributed brainstem network [565,566]. It is likely that the nasotrigeminal reflex is mediated via a highly redundant and anatomically distributed network mechanism. However, experimental evidence suggests that the synaptic interplay between the pontine (KF) and medullary (pre-BötC) has a pivotal role in the mediation of postinspiratory BH-D bradycardia and respirHRV [499,501,531].

5.5 Additional sensory mechanisms during short and prolonged breath-hold dives in animals and humans.

An important determinant for the initiation and expression of the diving bradycardia is water temperature. Cold water is enhancing the sensory input arising nasotrigeminal and trigeminal sensory inputs from the face and forehead. Consequently, the magnitude of the diving bradycardia is correlated with the decrease in water temperature [567,568]. Several individuals have been recorded with heart rates below 25 bpm [569-572] after facial immersion, demonstrating the strength of this reflex in temperatures ranging from 17°C to 0°C. Besides the direct effect of water temperature both volitional or reflex breath-hold suspends inspiration which in turn triggers a variety of secondary sensory reflex pathways that directly or indirectly further modulate CVT and the centralization of circulation to favor blood perfusion of vital organs during diving [481]. These secondary sensory reflex pathways involve predominantly pulmonary stretch receptor (see 5.1) and arterial oxygen sensors of the carotid body (5.2) which are all relayed in the NTS [573]. Importantly, the majority of afferent input to nA cardiac vagal motor neurons originates from the NTS [574] which further supports the significance of additional sensory mechanism for the synaptic gating of the diving bradycardia.

5.5.1 Lung stretch receptor (Hering Breuer reflex) mediated modulation of the diving bradycardia.

The Hering–Breuer inflation reflex is a respiratory reflex stimulates slowly adapting pulmonary stretch receptors [575] which are relayed via the vagus nerve to the NTS (see Kubin et al., 2006). The physiologic significance of the Hering-Breuer reflex is related to the sensory termination of inspiration and consequently the mediation of the respiratory phase transition from inspiration to postinspiration (early expiration) [576]. During diving the decrease in pulmonary stretch receptor activity during apnea in expiratory position, combined with cessation of central inspiratory neuronal drive, is an important integrative mechanism that promotes bradycardia [536,577] (Fig. 5.4).

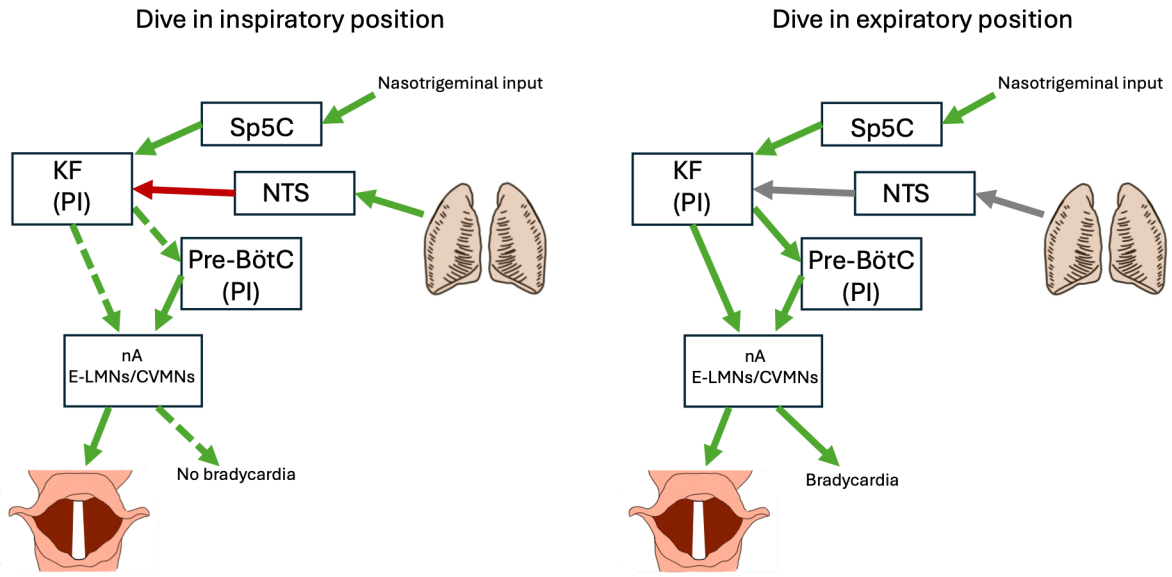

Figure 5.4. Diminished drive from lung pulmonary stretch receptors is enhancing the diving bradycardia.

Excitatory connections are represented as green arrows; inhibitory connections are depicted as a red arrow and neutral/or diminished the sensory input from pulmonary stretch receptors are illustrated as gray arrows. A breath-hold in inspiratory position is associated with tonic drive from pulmonary stretch receptors which provides inhibition of the KF in the pons [578], which in turn is causing a reduced descending excitation of the pre-BötC and CVMNs in medulla and is reducing the net expression of cardiac vagal tone towards the heart. Contrary absence or low drive from pulmonary stretch receptors allows for a rapid gating of the diving bradycardia. CVMNs: Cardiac Vagal MotoNeurons; E-LMNs: Expiratory Laryngeal MotoNeurons ; KF: Kölliker-Fuse; nA: nucleus Ambiguus; PI: Postinspiration; pre-BötC : pre-Bötzinger Complex; Sp5C : Spinal Nucleus of trigeminal Caudalis pars.

This secondary sensory modulation of the diving bradycardia can be also observed in human physiology. In prolonged static breath-hold, the progressive decrease in pulmonary stretch receptors feedback is related to small expiratory efforts (related to the release of small air bubbles) by the divers throughout the breath-hold dive. Thus, the progressive reduction of lung volume between the beginning and end of the breath-hold dive, is a mechanism that participates to the increase of bradycardia in correlation with dive duration [50]. The contribution of Hering-Breuer reflex is even more visible in deep dive exercises when changes in barometric pressure is compressing the lungs and consequently the lung volume [579], explaining the extreme

bradycardia seen in elite performers [580]. It is generally accepted that lung volume decreases by 66% and 75% at depths of 20m and 30m, respectively [581,582]. Heart rates below 30 bpm have been recorded in individuals at depths ranging from 19 to 97 meters [580,583-586]. Thus, there is a likely connection between pulmonary stretch receptors and facial receptors at depth, as colder water at greater depths may enhance the effects on CVT. At level of the brainstem a diminishing pulmonary stretch receptors feedback is potentially linked to a disinhibition of KF neurons which receive inhibition from either inspiratory neurons of the pre-BötC [491] or importantly from the pulmonary stretch receptor afferents [578].

5.5.2 Arterial chemoreceptor evoked modulation of the diving bradycardia

The chemoreceptors of the carotid body also play an important role in maintaining the level of bradycardia during prolonged dives and consequently progressive asphyxia [50,587-589]. The afferent feedback from the carotid body is, like the pulmonary stretch receptors, relayed in the nucleus of NTS and is utilizing the connectivity of the NTS to modulate the strength of the diving bradycardia specifically via projection neurons to KF [590], Fig 5.5. The precise mechanism are not experimentally verified but it is plausible that during diving the carotid body feedback may cause either sympatho-inhibition or is providing direct excitatory inputs the CVMNs of nA in the presence of nasotrigeminal afferent input [573].

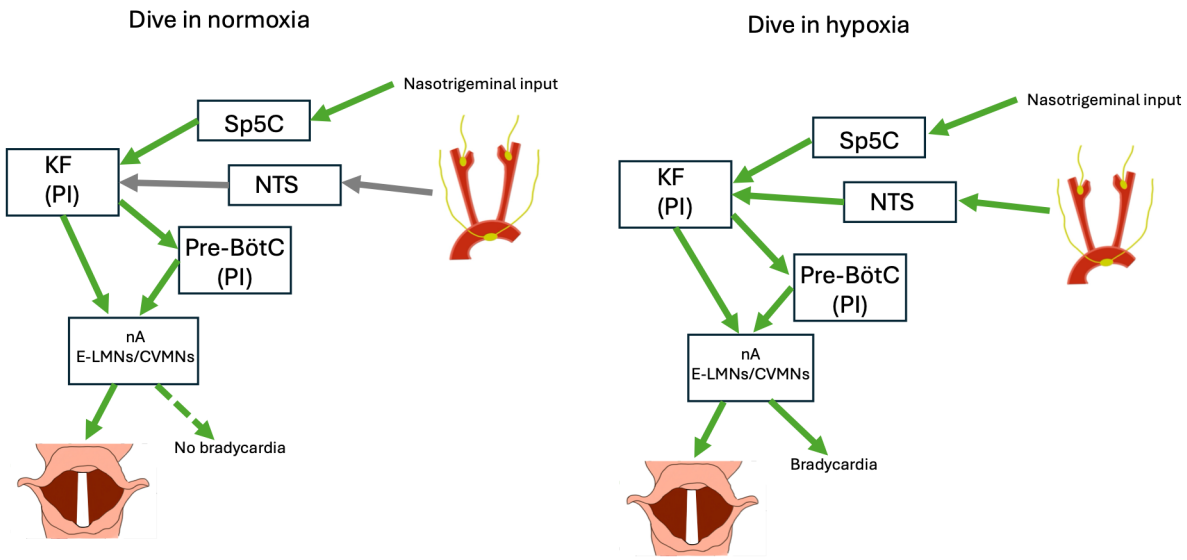

Figure 5.5. Chemoreceptors input facilitates the diving bradycardia.

Excitatory connections are represented as green arrows; and neutral sensory input from oxygen sensors of the carotid body is illustrated as gray arrows. The lack of oxygen uptake in the lungs

triggers progressive hypoxia which is sensed by the arterial chemoreceptor (e.g. carotid body) and drive form the carotid body afferent which is relayed in the nucleus of the solitary tract subsequently provides additional excitation to the circuit that mediates the cardiac sinus arrhythmia and the nasotrigeminal reflex. Together this is causing a well-documented increase of the strength of the initial diving bradycardia [591]. CVMNs: Cardiac Vagal MotoNeurons; E-LMNs: Expiratory Laryngeal Motoneurons; KF: Kölliker-Fuse; nA: nucleus Ambiguus; PI: Postinspiration; pre-BötC : pre-Bötzinger Complex; Sp5C : Spinal Nucleus of trigeminal pars Caudalis.

In humans the contribution of carotid body feedback during hypoxia can be observed during static apnea where progressive hypoxia is strongly correlated with an increase in CVT measurements like the high frequency domain of heart rate variability and mean Square of Successive RR Interval Differences [50,592].

5.6 Learning how to elicit a diving bradycardia.

In the following paragraph we develop a hypothesis how learning based on synaptic potentiation within brainstem circuits that mediate the diving bradycardia and respirHRV can explain training related improvement of the expression of the diving bradycardia and overall CVT.

Panneton & Gan (2020) [481] have shown that the physiologic features of the diving response are similar in animals during voluntary and involuntary (trained or untrained animals) submersion. The lacking difference in the expression of the diving bradycardia strongly suggests that the core brainstem circuit the control CVT is recruited in a similar fashion during both voluntary and reflex initiated dives. However, in humans the expression of the diving bradycardia during BH-D depends on regular training and thus both the initiation and expression of a diving bradycardia and thus an indirect volitional control of cardiac vagal activity can be learned.

We postulate that during diving the co-activation of nasotrigeminal sensory input and volitional breath-hold that gates the expression of the diving bradycardia (see chapter 3) is primed to trigger Hebbian plasticity [593,594]. The latter is causing a potentiation of synaptic activity and consequently the strengthening of synapses within the brain circuits that mediate the diving bradycardia (Fig. 5.6). The gating of the diving bradycardia by volitional breath-hold

is difficult to study in experimental settings. However, as a proof of principal it was experimentally shown that the gating and expression of the diving bradycardia can be modulated by classic Hebbian learning paradigms. Here repetitive co-stimulation of nasotrigeminal and arterial chemoreceptor afferent can progressively enhance the strength of the diving bradycardia in absence of the chemoreceptor stimulus [591]. However, such hypoxia related mechanisms may only occur during extreme durations of breath-hold dives and consequently in association with significant PO_2 desaturation of the arterial blood. Therefore, Hebbian plasticity may only contribute to the expression of extreme diving bradycardia observed in performance of elite divers [50,595]. Nevertheless, in recreational divers a short period of static BH-D training can yield a faster onset and increased magnitude of the diving bradycardia [596,597] suggesting that the gating of diving bradycardia in humans must be learned with in subconscious brainstem circuits.

The effect of physical activity and exercise on synaptic long-term potentiation as the cellular substrate of learning [598] was already discussed previously [599,600] and could therefore also apply for BH-D exercises. Cellular mechanisms of learning and memory formation in the CNS are for decades closely associated with the function of glutamatergic N-Methyl-D-Aspartate receptors (NMDA-R) [601,602] and these receptors are also specifically present on neurons that mediate the nasotrigeminal reflex [603] (Fig. 5.6). NMDA-R are predominantly involved in synaptic processing in the trigeminal relay of in Sp5C nucleus and the KF in pons, and less present in neurons that mediated the diving response in the NTS, pre-BötC, and Bötzinger Complex [603]. Specifically, in the KF, NMDA-R are abundantly expressed [531,604] and blockade of NMDA-R disrupts the nasotrigeminal breath-hold and largely diminishes the expression of the diving bradycardia [531]. Moreover the KF receives synaptic input is from the nasotrigeminal relay in the Sp5C [553,554] as well as from NTS as relay for sensory drive from pulmonary stretch receptor and carotid body chemoreceptors [590,605,606]. The anatomical connectivity and the presence of a high density of NMDA-R suggest that the KF may play a pivotal role for synaptic plasticity required for a learning process that improves the gating the diving response. This hypothesis is further supported by data showing NMDA-R mediated synaptic potentiation at the cellular level [607]. In summary, we postulate that the gating and expression of the diving bradycardia can be learned with regular BH-D exercise and likely involve NMDA-R dependent mechanisms in the brainstem.

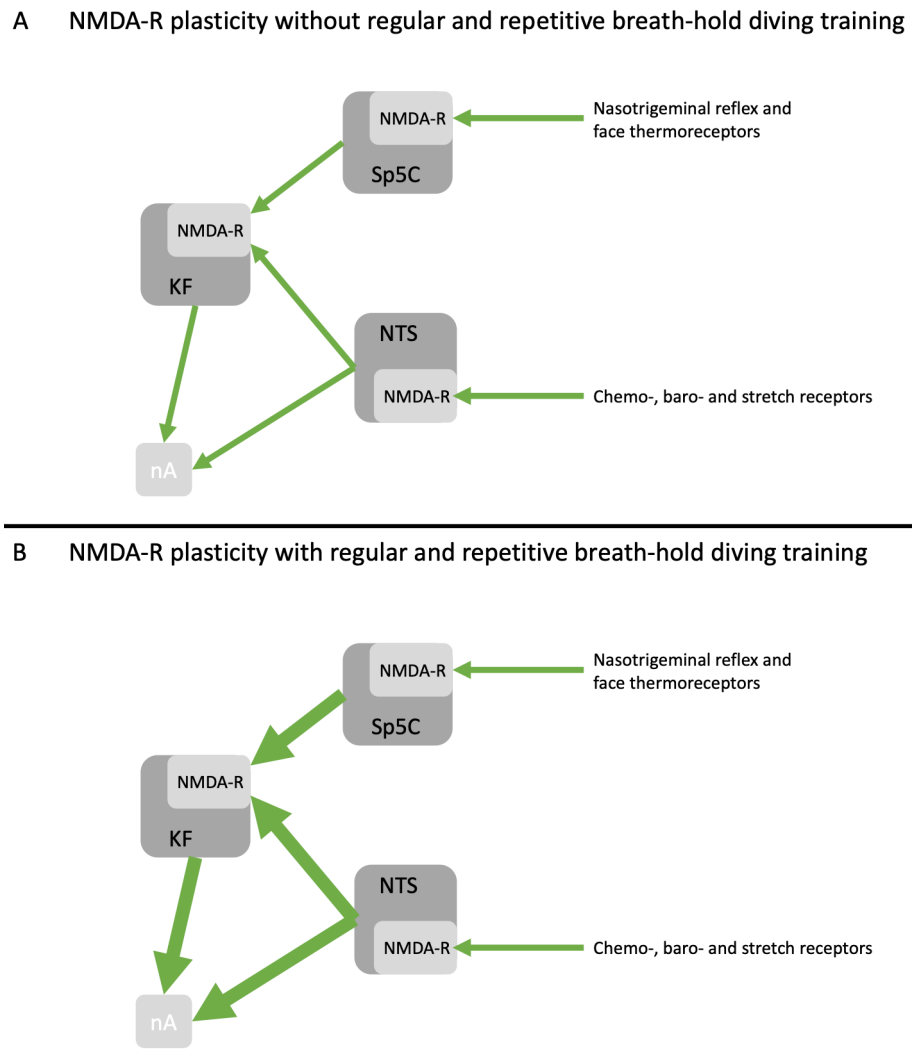

Figure 5.6. NMDA-receptor plasticity associated with diving exercise.

Excitatory connections are shown as green arrows. (A) Irregular training exercises of breath-hold diving do not lead to plasticity associated mediated synaptic potentiation and thus do not improve the gating of the diving bradycardia and general cardiac vagal tone. (B) In contrast, repeated (multiple series of breath-hold diving per session) and regular (several times a week) breath-hold diving exercises will lead to NMDA-R mediated strengthening of the synaptic contacts (bold green arrows) triggered by synaptic potentiation within in the brainstem circuit that regularly mediates the diving response. Since the same circuitry also generates the respiratory sinus arrhythmia regular dive training provides a tool to improve overall cardiac vagal tone in healthy human subjects and is an appropriate non-invasive tool to improve cardiac vagal tone in patients in patients. KF: Kölliker-Fuse; NTS: Nucleus Tractus Solitarii; nA: nucleus Ambiguus; NMDA-R: N-Methyl-D-Aspartate receptors; Sp5C: Spinal trigeminal nucleus pars caudalis.

5.7 Evidence for health benefits linked with regular Breath-hold dive exercise.

Athletes practicing aerobic activities such as running, biathlon and cycling, display cardiac hypertrophy which is associated with a significant resting bradycardia and is commonly coined as the "athlete's heart syndrome" [608]. Breath-hold divers exhibit only minor structural modifications (of the right ventricle), linked to increase of venous return caused by peripheral vasoconstriction during prolonged dives [609]. Nevertheless, the minor structural modifications are sometimes associated with ECG abnormalities (supraventricular couplets and triplets, transient first- and second-degree atrioventricular block, and sinoatrial block) [609]. However such ECG irregularities are also commonly observed in highly trained athlete [608]. However, unlike endurance athletes regular subjects that perform regular breath-hold dives do not exhibit a resting bradycardia seen in endurance sport athletes [610]. Breath-hold divers display a resting heart rate between 60 and 80 bpm [611-616] which resemble standard values for healthy individuals [617]. However, short-term resting measures show that the rMSSD values in breath-hold divers are higher [618] compared to the short-term reference values for healthy individuals [72]. In long-term variation values (24h ECG recording), regular diving exercise increases rMSSD, enhance the high frequency component of heart rate variability and lower minimal HR compared to a healthy sedentary group (Table 5.1).

Table 5.1. Long-term (24 h) variation of cardiac vagal tone in divers

Subjects (*ref*)	**Cardiac vagal tone metrics**
Elite divers	
n=13 [103]	**mean HR 66.7±4.3 bpm**, **min HR 37.6±2.7 bpm**, max HR 128.2 ± 14.5 bpm, mean **rMSSD 44.5 ± 11.7 ms, and mean HF 521.2 ± 251.9** ms^2
n=16 [609]	mean HR 69.5 ± 1.7 bpm, **minimal HR 42.3 ± 1.0 bpm**, and maximal HR 132.8 ± 4.6 bpm
Healthy sedentary	
n=13 [103]	mean HR 80.5±5.7 bpm, min HR 46.6 ± 5 bpm, max HR 139 ± 14.1 bpm, mean rMSSD 27.6 ± 7.8 ms, and mean HF 297.9 ± 212.6 ms^2
n=16 [609]	mean HR 70.2 ± 1.1 bpm, minimal HR 48.8 ± 1.7 bpm**,** maximal HR 131 ± 3.5 bpm

BPM: Beats Per Minute; HR: Heart Rate; ms: milliseconds ; rMSSD: root Mean Square of Successive RR Interval Differences.

The long-term data observed in recreational breath-hold divers (Table 5.1) show higher rMSSD and identical HF compared to reference measures for healthy individuals [71,476,619]. Such profound rMSSD changes can be only partially reproduced with other breathing techniques, such as the Wim Hof method. This technique involves taking cold baths and, either simultaneously or separately, performing hyperventilation followed by maximal apnea at the end of expiration. A study showed that after 10 days of practice, the long-term variation of rMSSD decreased from 28.08 ms to 25.77 ms in 13 subjects [620]. However, these data are not comparable to values seen in divers (Table 5.1). Overall an increase in rMSSD appears to be specific to breath-hold exercises, excluding end-expiratory breath-holds [540,571,613] and both increasing or decreasing respiratory frequency reportedly reduced rMSSD [46,128,621,622]. Finally, when comparing the baseline heart rate with the heart rate after recovery from a breath-hold dive, individuals retain increase vagal tone for at least a few minutes after the session [623-625].

5.8 Therapeutic potential of breath-hold diving

CVT is a clinical indicator of overall health and a low value of CVT is corresponding to a higher risk of mortality [15]. Indeed CVT is reduced in many diseases such as depression [626], type 2 diabetes mellitus [627], and generally in inflammatory diseases [628], causing a shift of sympatho-vagal balance in HRV towards sympathetic cardiac tone. A strong dominance of the cardiac sympathetic system and is seen as predictor of cardiovascular mortality [15], Covid-19 mortality [629,630] and in particular in cancer mortality [17,23,24,631].

Regular BH-D exercise yields a higher CVT and ortho-sympathetic balance [103] compared to reference measurements for healthy individuals [71,476]. Thus, we suggest that by increasing CVT with regular, monitored and supervised BH-D exercise can help to harness a permanent increase in CVT and can therefore effectively contribute to alleviation of oxidative stress, inflammation, sympathetic hyperactivity, and chronic hypoxia [25,632] seen in many diseases.

However, the translation of breath-hold diving into clinical oncology practice raises legitimate questions of feasibility that must be addressed before this approach can be proposed as a structured therapeutic intervention. Cancer patients – particularly those undergoing chemotherapy or radiotherapy – often present with significant comorbidities, reduced functional capacity, peripheral neuropathy, cardiotoxicity, and altered respiratory mechanics, all of which may constrain the type and intensity of breath-hold exercises that can be safely performed. Elderly patients, who represent a substantial proportion of oncology populations, may additionally exhibit blunted chemoreceptor sensitivity, reduced pulmonary compliance, and cardiovascular fragility that warrant individualized risk assessment prior to any apnea-

based protocol. Importantly, breath-hold diving as a vagal stimulus does not require the performance of extreme apnea or underwater diving. Static dry apnea – performed in a supine or seated position, without water immersion – constitutes a minimal-intensity entry point that can be adapted to deconditioned patients. The brainstem mechanisms described in this chapter can be engaged even with modest breath-hold durations of 15–30 seconds, provided the exercise is repeated regularly across sessions. Facial immersion in cold water, which potentiates the nasotrigeminal reflex and substantially amplifies the diving bradycardia, represents an intermediate step that could be integrated in a stepwise protocol once dry apnea is tolerated. Compared to other autonomic modulation techniques such as guided slow breathing or HRV biofeedback – which have a more established evidence base in clinical settings – breath-hold diving offers the advantage of simultaneously engaging multiple synergistic brainstem pathways (trigeminal, pulmonary stretch receptor, chemoreceptor), potentially yielding a stronger and more durable CVT response. That said, these two approaches are not mutually exclusive, and a phased protocol combining slow-breathing techniques in early treatment phases with progressive introduction of supervised breath-hold exercises during recovery could represent a pragmatic clinical pathway. Dedicated feasibility trials in oncology patients, with careful monitoring of HRV, oxygen saturation, and symptom burden, are urgently needed to establish safe and effective exercise parameters for this population.

The brainstem mechanisms described in Chapter 5 establish that CVT can be meaningfully and durably enhanced through structured breath-hold exercise. But before this can be proposed as a therapeutic strategy in oncology, a critical question must be addressed: does vagal activity uniformly protect against cancer, or does its role vary depending on tumor location and the direction of vagal signaling? Chapter 6 confronts this ambivalence directly, distinguishing the potentially pro-tumoral effects of chronic afferent overstimulation from the anti-tumoral potential of efferent enhancement.

6. Chapter 6: The forgotten role of the vagus nerve in cancer?

This Chapter is essentially drawn from:
Martinez P, Sabatier JM. Malignant tumors in vagal-innervated organs: Exploring its homeostatic role. Cancer Lett. 2025 May 1;617:217539. doi: 10.1016/j.canlet.2025.217539.

General abstract and Key Points of the Article :

This chapter serves as the point of convergence and synthesis of the knowledge accumulated over several years of research in onco-rythmology. In fact, this article seeks to highlight that the physiology of the vagus nerve is sometimes misunderstood, in some cases even forgotten, and in others, grossly extrapolated. Many researchers interested in neurobiology and tumor-central nervous system communication sometimes overlook the fact that the primary role of the vagus nerve is a sensory one, and mostly only mention the spinal fibers. Additionally, the vagus nerve interacts closely with several key regulatory systems, such as the microbiome and the renin-angiotensin system. Thus, this article challenges our current understanding of the vagus nerve, and here are the key points addressed:

- Vagal afferent fibers possess a variety of receptors capable of capturing signals from the tumor microenvironment (which is itself induced by metabolic alteration), compared to spinal fibers.
- Afferent fibers can transmit alterations in the microbiome and pro-inflammatory activation of the renin-angiotensin system in cancers with direct vagal innervation.
- Activation of vagal afferent fibers can lead to inhibition of efferent vagal fibers and activation of the sympathetic system.
- This inhibition leads to an increase in intestinal dysbiosis, a decrease in CVT, an increase in renin, and thus the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic axis, as observed in most cancers.

Thus, this article highlights that tumor metabolic stress induces the creation of the environment necessary for tumor progression, and that afferent fibers may participate in this process. Therefore, it becomes strategic to stimulate the efferent fibers that will be naturally inhibited by the constant metabolic and immune stress, and breath-hold diving could thus represent a relevant strategy.

6.1 Introduction

Cancer remains a significant global public health challenge, with 19.3 million new cases and 10 million deaths reported annually [633]. Despite research investments exceeding $24 billion between 2016 and 2020, this multifactorial disease continues to challenge the scientific community due to the complexity and ambiguity of its underlying mechanisms [218,634]. Recent studies have highlighted the potential involvement of the ANS in cancer development and progression [635], sparking significant interest despite ongoing contradictory findings in the field. For example, research suggests that vagus nerve signaling can inhibit tumor progression by modulating immune responses, thereby reducing peritoneal metastasis [636]. However, other findings reveal that the influence of the vagus nerve varies across cancer types: vagotomy reduces tumor proliferation in gastric and colorectal cancers but appears to promote tumor growth in pancreatic and prostate cancer, illustrating the complexity of this interaction [637]. Some researchers argue for a significant role of nerves in shaping the tumor microenvironment, while others remain skeptical due to experimental limitations or lack of reproducibility. This skepticism was further heightened by the retraction of the 2019 Nature Neuroscience study [638]. Our review aims, to focus on the underexplored role of vagal afferent fibers in transmitting tumor-derived signals to the CNS, potentially influencing systemic disease progression. With approximately 80% of its fibers being afferent, the vagus nerve is equipped with a remarkable diversity of receptors capable of detecting immune, metabolic, mechanical, and chemical signals, positioning it as a critical mediator between tumors and the CNS. We explore complex interactions involving the vagus nerve, the gut microbiota, and the renin-angiotensin system (RAS) which converge in integrative centers, which could modulate tumor-related signaling. Additionally, we examine the efferent pathways of both the sympathetic and parasympathetic systems, addressing their controversies and exploring their impact on tumorigenesis, as well as the role of chronic cancer-related stress in driving tumor progression through neuro-immune-endocrine and sympathetic pathways. By highlighting the limitations of current studies and suggesting experimental improvements, this study could pave the way for innovative therapeutic strategies–such as targeting vagal afferents in organs directly innervated by it, targeting integrative autonomic centers like the PVN, or even stimulating systemic vagal efferent fibers. This review seeks to contribute to a deeper understanding of the neuro-oncological mechanisms in cancer and their potential translational applications.

6.2 Afferent tumor-CNS pathways

To identify the nerve structures that facilitate communication between the tumor and the central nervous system, it is essential to define the various stimuli that can activate them. This requires an understanding of the environment in which the tumor develops, known as the "tumor microenvironment." This microenvironment is highly heterogeneous and consists of several components, including a hypoxic niche, an acid-base niche, a nerve niche, metabolic variations, an immune microenvironment, and mechanical pressures [639]. The ANS maintains homeostasis by regulating its constants and various functions.

6.2.1 Spinal sensory neurons

Paradoxically, spinal sensory neurons might contribute to a wider range of cancers than the vagus nerve, as their reach also extends peripherally. Spinal afferent nerves contain C-type fibers, similar to the vagus nerve [640,641], and Aδ-fibers [642]. Generally, spinal afferents have fewer C fibers than the vagus nerve [643,644]. Several studies have shown that jugular neurons and dorsal root ganglia (DRG) have similar sensory neurons that respond to nociceptive and mechanical stimuli [644,645]. Spinal afferents also contain receptors (acid-sensing ion channel (ASIC), P2X, and transient receptor potential vanilloid type (TRPV)) that respond to temperature changes, pH variations, and mechanical stress, all of which are typically associated with pain [646,647] whose main neurotransmitters are substance P and calcitonin gene-related peptide (CGRP) [648]. Spinal sensory neurons also express proton-activated G protein-coupled receptors (GPCRs), particularly GPR65. GPR65 is expressed in the CNS and dorsal root ganglia neurons [649], where it detects changes in extracellular pH. In cancer, spinal afferent nerves could be stimulated by the microenvironment, primarily through pain-related signals: cold/heat thermoreceptors, low pH, and pressure [645,650-652]. However, pain is present in less than one out of two cancer patients [653]. However, some characteristics of the microenvironment may be communicated through pro-inflammatory cytokines, such as tumor necrosis factors (TNF-α) and interleukin 1β (IL-1β)[654].

6.2.2 Vagal Sensory Afferents: An Underexplored Pathway for Tumor-CNS Communication?

The vagus nerve acts as a gatekeeper [1] and works closely with the endocrine and immune systems [2,3]. It is composed of 80% afferent fibers (sensory fibers) and 20% efferent fibers (motor fibers) [655-657]. Afferent fibers contain 85% type C fibers and the rest are type A-Delta fibers [657]. Type C fibers are sensory and polymodal and can respond to various stimuli of thermal [658], mechanical, chemical [657,659], osmolarity [660,661], immune [662] and nociceptive [640,654]. Mainly in the gustatory, gastrointestinal, cardiovascular, and respiratory systems. The jugular neurons of the vagus nerve largely correspond to the somatosensory neurons of the dorsal root ganglia (DRG), specifically mechanoreceptors and chemoreceptors. Meanwhile, the nodal neurons of the vagus nerve contain the majority of the polymodal type C fiber neurons mentioned earlier, including chemo-, baro-, stretch-, tension-, and volume-sensors [644]. Surprisingly, despite the fact that the majority of its fibers are sensory, most studies do not take the vagus nerve into account when analyzing sensory neurons in cancer [635,663,664]. Especially considering that it contains a greater plurality of sensory neurons and includes the exact same types of neurons as spinal fibers in its jugular portion [644]. Recent studies [648,665,666] have begun to illuminate potential links between vagal afferent fibers and tumor biology, though direct evidence connecting these pathways to CNS-tumor communication remains limited. In this section, we synthesize findings on vagal sensory receptors and their potential roles in detecting changes in the tumor microenvironment. By drawing on these studies, we propose plausible mechanisms through which vagal afferents may transmit tumor-derived signals to the CNS. Rather than providing an exhaustive review, this work deliberately focuses on a broader range of receptors potentially involved in transmitting signals from the tumor microenvironment, beyond those already well-documented for inflammation and nociception [648]. This approach aims to address specific gaps in the literature and highlight underexplored mechanisms that may contribute to tumor-CNS communication.

6.2.3 Inflammation, Cytokines, and Cancer Progression

The vagus nerve plays a pivotal role in immune response modulation, primarily through its afferent fibers. Studies have shown that intraperitoneal administration of TNF or IL-1β in mice triggers specific compound action potentials in the vagus nerve, highlighting cytokine-specific alterations in vagal activity [667]. These patterns disappear in genetically modified mice lacking TNF-α or IL-1β receptors or in those with surgically transected vagus nerves, demonstrating the critical role of afferent fibers in transmitting peripheral immune signals to the brain. Macrophages, which can constitute up to 50% of the tumor mass [384], release molecules like TNF-α and IL-1β that can stimulate the vagus nerve [654,668-670]. Furthermore, electrical stimulation of vagal afferent fibers has been shown to induce IL-1β expression in the brain and activate the hypothalamic-pituitary-adrenal (HPA) axis, emphasizing the vagus nerve's role in systemic immune modulation [671,672].

6.2.4 Vagal Sensory Receptors Potentially Transmitting Tumor Microenvironment Information

pH

The pH and oxygen levels are altered in the tumor microenvironment. Tumors generally evolve in an acidic extracellular environment. In normal differentiated cells, intracellular pH is typically between 6.9 and 7.2, while extracellular pH is between 7.2 and 7.4. Nuclear magnetic resonance imaging studies have measured the extracellular pH of tumors and found it to be between 6.2 and 6.8, whereas the intracellular pH of cancer cells is between 7.2 and 7.7 [403-405]. The vast majority of vagus nerve fibers contain nociceptors, such as TRPV1 receptors that can be activated by severe extracellular acidification [673] as well as ASIC receptors [674]. The vagus nerve also contains the GPR65 receptor, which is activated during extracellular pH acidification [675], with a maximum activation threshold at pH 6.5 [676], corresponding to the mean pH extracellular levels found in the tumor microenvironment.

Hypoxia

Regarding oxygen content, hypoxia is one of the markers of the microenvironment. Tumor cells are exposed to a gradient of oxygen concentrations: the further cancer cells are from large vessels, the more hypoxic the environment becomes [412,413]. Thus, larger tumors are in hypoxic environment, peripheral chemoreceptors, particularly vagal ones, could be stimulated [677]. The

vagus nerve contains transient receptor potential ankyrin A1 (TRPA1), which are sensitive to O2 variations [678] and hypoxia, these receptors are present in tumoral microenvironment [679].

Temperature and Pressure

The vagus nerve also contains thermoreceptors [658], and the temperature in the tumor environment is generally slightly higher than in a healthy environment, by about 1°C [418]. A number of thermosensitive were discovered in the sensory vagus nerve including TRPV1, transient receptor potential melastatin 8 (TRPM8), and TRPA1 [644]. Pressure and tissue deformation are characteristics of tumors. This is due to the high osmotic pressure in tumors, mostly resulting from tumor debris and an increase in extracellular matrix components. These general characteristics are identical in the tumor microenvironment of different cancers [391]. The high osmotic pressure in tumors is consistent with the high pressure of fluids, namely interstitial fluid, blood, and lymph [392,393]. This information could be transmitted by vagal mechanoreceptors [680]. The afferent vagal branches of the gastrointestinal tract contain mechanoreceptors such as Oxtr+ and Glp1r+ [681].

Metabolism, nutrients and hormones

Various metabolic pathways, including glucose metabolism, amino acid metabolism and fatty acid metabolism are at play during tumor growth. Vagal afferent fibers can relay information on levels of metabolic molecules and hormones regarding lipids, cholecystokinin, leptin, peptide YY, insulin, and glucose to higher centers [665,668,682,683]. These signals are transmitted through a variety of receptors, including Cholecystokinin: CCK1, CCK2, CCK-A; Leptin: LRb; Ghrelin: GHSR1a; Glucagon-like peptide 1 receptor: GLP-1R, and Peptide YY: Y2 [684,685]. A subset of neurons in the nodose ganglia and gastric vagal afferents are glucoresponsive with Glucose Transporter 3 (GLUT3), Glucokinase (GK), and ATP-sensitive potassium (KATP) channels [686]. The two main metabolic pathways used by cancer cells are aerobic glycolysis (also known as the Warburg effect) [687] and glutaminolysis [326,688]. Glucose induces the release of 5-hydroxytryptamine (5-HT) from enteroendocrine cells, which, in turn, activates 5-HT3 receptors on the peripheral terminals of gastrointestinal vagal sensory nerves, generating a vagal afferent signal that can be amplified or prolonged [689]. The GPR65 receptor is also involved in the detection of intestinal nutrients [675]. These homeostatic signals–leptin, ghrelin, insulin, and glucose–are associated with obesity [690], which in turn is associated with 13 types of cancer [691]. The vagus nerve is involved in systemic glycemic regulation [692]. A small subset of vagal afferent

neurons in the duodeno-intestinal region contains receptors that are sensitive to glutamine [693], the second fermentable fuel for cancer cells. Vagal afferent fibers also possess receptors that are sensitive to glutamate increases in key regions of the digestive system, including the stomach, intestine, and hepatoportal area [694]. Vagal afferent fibers can contribute to communication between the CNS and the tumor and indirectly to pathophysiological conditions, as they may play a role in metabolic syndrome through sympathetoexcitation. Studies suggest that these fibers are crucial in mediating peripheral sympathoexcitation, which can lead to metabolic disturbances such as insulin resistance, liver steatosis, and altered adipose tissue thermogenesis [695]. Vagotomy in vivo, reverses the metabolic reprogramming reflected by metabolic switch from glutaminolysis to OxPhos/glycolysis and normalization of the energy metabolism in cancer cells [696].

The cells of the tumor microenvironment overexpress the same receptors as those found on the surface of the vagus nerve in tumors in vagal-innervated organs. As previously discussed above, receptors expressed on vagal fibers–such as TRPV1, TRPA1, GPR65, Oxtr+, and GLP-1R–are also overexpressed in many tumors in vagal-innervated organs. GPR65, a receptor responsive to extracellular acidification, is highly expressed in cancers of vagally innervated organs such as the esophagus, stomach, kidneys, and pancreas [697]. Bagchi et al. indicate that GPR65 on tumor-associated macrophages drives tumor growth, particularly in the context of obesity. This highlights the receptor's potential role in linking the acidic microenvironment of tumors with immune modulation and metabolic dysregulation [698]. TRPA1, another key receptor, responds to hypoxic conditions within tumors and is overexpressed in cancers such as cholangiocarcinoma, head and neck cancers, renal cancers, and lung cancers [699]. Likewise, Oxtr+ receptors, associated with mechanosensation, are overexpressed in cancers of the lungs, uterus, heart, and pancreas [700]. GLP-1R, involved in glucose metabolism, is highly expressed in cancers of the pancreas, stomach, and respiratory tract [701]. Together, these receptors could enable vagal afferent fibers to detect and transmit biochemical and mechanical changes in the tumor microenvironment, contributing to systemic immune and metabolic regulation.

The vagus nerve may not convey all features of the tumor microenvironment in every type of cancer, as this transmission can vary depending on the tumor's location. Consequently, Table

6.1 below outlines the specific characteristics of the tumor microenvironment that may be transmitted according to their respective locations.

Table 6.1. Potential Sensory Stimuli from the Tumor Microenvironment Transmitted via the Vagus Nerve

Organ	Sensory Stimuli for Tumor Microenvironment Signal Transmission											Réf
	O_2	CO_2	pH	T°	TNF-α / IL-1β	Str/V R	Osm	Pres	Nutr	Met / Horm	Chem	
Heart (aortic body)	Low	High	Low		Yes/Yes							654,702,703
Airways and lungs	Low		Low	High	Yes/Yes	Yes/Yes						644,654,680
Oesophagus			Low		Yes/Yes	Yes/No	High					654,680,704
Gastric			Low		Yes/Yes	Yes/No	High		Yes	Yes		654,668,680,693,694,704
Small intestine					Yes/Yes	Yes/No			Yes	Yes		654,668,680,693,694
Large intestine					Yes/Yes	Yes/No			Yes	Yes		654,668,680,694
Liver					Yes/Yes		Yes			Yes		654,668,680,694,705,706
Pancreas			Low	High	Yes/Yes			Yes			Yes	707
Kidneys					Yes/Yes							654,708,709

Legend: Y: Yes; N: NoO_2: O_2 levels; CO_2 levels; pH: Extracellular pH; T°: Temperature; Lact: Lactate variation; Str/V R: Stretch / Volume receptors; Osm: Osmolarity; Pres: Pressure; Ins: Insuline sensing; Nutr: Nutrients volume; Met/Horm: Metabolites and hormones (cholecystokinin, glucagon-like peptide 1, ghrelin, leptin, glucose, glutamine, glutamate, lipids, peptides); Chem: Chemical sensing (trypsin, cholecystokinin, secretin, arginine vasopressin, serotonin, histamine, bradykinin, vascular endothelial growth factor, prostaglandins, adenosine triphosphate)

In summary, vagal afferents could be stimulated by many characteristics of the tumor microenvironment [658]. Evidence suggests a potential link between tumors in organs innervated by the vagus nerve and the stimulation of its afferent fibers. However, this connection remains largely underexplored in the scientific literature.

Moreover, vagal afferent fibers also play a role in influencing treatment-related side effects. Indeed, a study [710] demonstrates that cisplatin activates gastrointestinal afferent fibers via 5-HT3 receptors, leading to common side effects such as vomiting and reduced appetite, while sparing fibers in the portal vein and liver. This indicates that the side effects arise from localized activation in the gastrointestinal tract rather than from systemic vagal activation. Investigating how these afferent fibers transmit signals related to disease and treatment could offer valuable insights into mitigating chemotherapy side effects by specifically targeting relevant nerve pathways. Another study showed that cisplatin-induced activation of mesenteric afferents is primarily vagal under normal conditions and depends on 5-HT_3 receptors. However, after vagotomy, alternative non-vagal mechanisms (likely spinal afferent fibers) and 5-HT_3 receptor-independent pathways take over [711].

In brief, in this section, we examined the receptors expressed in tumors directly innervated by the vagus nerve, as well as those on vagal fibers that could mediate communication between the tumor and the brain. This underappreciated research avenue highlights the potential role of the vagus nerve, through its sensory afferents, as a unique pathway for tumor-central nervous system communication.

6.3 Interplay Between the Vagus Nerve, Microbiome, and Renin-Angiotensin System (RAS) in tumors in vagal-innervated organs

The three systems – the vagus nerve, the microbiome, and the RAS – could interact in a complex manner to regulate several aspects of human biology, particularly in the context of cancer. Each of these systems appears to exert a significant influence on tumor progression, inflammation, and metabolic alterations associated with cancer. However, it is their mutual interaction that reveals a dynamic and bidirectional network, where changes in one of these systems can modulate the others, thus creating an environment conducive to carcinogenesis or preventing tumor progression. These interconnections warrant a deeper exploration to better understand their role in cancer and to consider new therapeutic strategies targeting multiple pathways simultaneously.

The Microbiome, Cancer, and the Vagus Nerve

The vagus nerve serves as a crucial pathway for communication between the microbiome, the RAS, and the CNS, forming part of the tumor-CNS axis. Diet and water quality are significant contributors to gut microbial diversity, affecting both alpha and beta diversity [712,713,714,715]. Given that 80% of vagal fibers are sensory and afferent, the vagus nerve is the primary nerve innervating the gastrointestinal system, serving as a key conduit for bidirectional communication between the microbiota and the brain [716]. The vagus nerve is essential for the gut-brain connection, serving as the primary pathway through which the gut microbiota exerts its influence on the CNS. Vagal afferent fibers detect microbiota-derived signals through a variety of specific receptors, including Toll-like receptor 4 (TLR4), short-chain fatty acid (SCFA) receptors, TRPA1, and 5-HT receptors [717]. This sensory information is then relayed to the CNS. At contrary, the vagus nerve effects on CNS are suppressed by vagotomy [718,719]. The microbiome can contribute to carcinogenesis, tumor progression, and metastasis [720]. In colon cancer, pro-inflammatory cytokines and bacterial toxins can damage mitochondria [721], leading to chronic inflammation and genomic instability [722]. Cancer is generally associated with dysbiosis of the microbiome, where the microbiome can either promote or inhibit carcinogenesis depending on its state [723,724].

The Renin-Angiotensin System, Cancer and the Vagus Nerve

The RAS is another critical system in systemic adaptation, with dual pro- and anti-tumorigenic effects. Angiotensinogen, secreted by the liver, is cleaved by renin to form inactive angiotensin I, which is then converted into angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE), primarily secreted by the liver and acting in the lungs. Ang II binds to angiotensin receptors 1 and 2 (AT1R and AT2R) [725], with approximately 15 times more affinity for AT2R [726]. Aortic glomus cells are sensitive to Ang II via AT1R, providing information about the body's water and electrolyte balance [727]. Studies have shown that AT1R receptors are present in the afferent fibers of the vagus nerve, including at their peripheral terminals. These receptors are found not only in the vagal ganglia (such as the nodose ganglion) [728,729] and the vagus nerve trunk but also in the terminal regions of peripheral fibers that innervate various organs [730]. The bidirectional transport of these receptors allows their movement between these different regions, with anterograde transport and retrograde transport [731]. This suggests that AT1R receptors in peripheral terminals play a role in regulating vagus nerve responses. Ang II seems to have little effect on vagal afferent fibers but primarily affects vagal efferent fibers or sympathetic fibers [732]; we will revisit these effects in Section 3. AT1R is also present in the

DRG, the spinal cord, and the spinal nerves [733,734]. Additionally, vagotomy has been shown to increase plasma renin activity [735], and one animal study, in dogs, demonstrated that bilateral cervical vagotomy raises the concentration of ang II in systemic circulation [736]. AT1R is associated with pro-inflammatory, pro-angiogenic, and pro-tumorigenic effects, while AT2R produces opposing, anti-tumoral effects. Although angiotensin 1-7 also exhibits anti-tumoral properties, it is less common and thus not the focus of this discussion [737], which is why throughout the article we will only refer to AT1R for its pro-tumoral effects. AT1R contributes to cancer progression by promoting vasoconstriction, vascular compression, hypoxia, and acidosis, as well as targeting cancer stem cells [738,739]. Dysregulation of the RAS leads to overactivation of the ANG II-ACE-AT1R axis, which exacerbates insulin resistance, elevates blood glucose levels [740], and contributes to obesity and metabolic syndrome–well-established cancer risk factors. AT1R is overexpressed on the cell membrane in many cancers [741], and also in tumor-associated macrophages (TAMs) which are implicated in metastases [742]. Overexpression of AT1R in cells leads to the overactivation of the NADPH oxidase enzyme NOX, which induces the opening of mitoK(ATP) channels and increases ROS production [743]. The overexpression of mitoK(ATP) channels also increases matrix volume through osmotic changes [744], leading to matrix swelling and collapse of the mitochondrial cristae [745,746]. These features are similar to those observed in cancer cells [270].

Interactions Between the Microbiome and Renin-Angiotensin System

The microbiome and RAS exhibit bidirectional interactions. Gut bacteria and their metabolites influence both gastrointestinal and systemic RAS activity, while changes in the RAS affect microbiome composition and metabolic activity [747]. Both systems are often disrupted in cancers.

A Unified Role in Cancer? Exploring Synergistic Mechanisms

While we lack direct evidence demonstrating the simultaneous involvement of the vagus nerve, the microbiome, and the RAS in tumor progression, the table 6.2 below highlighting the state of the RAS and the microbiota in tumors in vagal-innervated organs.

Table 6.2. Status of the renin-angiotensin system and the microbiome in tumors in vagal-innervated organs. AT1R: angiotensin type 1 receptor

Organ	Overexpression of AT1R	Dysbiosis	Bacteria associated with tumor
Airways and Lungs (tissue)	Yes [748]	Yes [749]	Escherichia coli, Staphylococcus epidermidis and Haemophilus influenzae [750-752]
Esophagus	Yes [753]	Yes [754]	↑Tannerella forsythia, Streptococcus anginosus, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum [755]
Gastric	Yes [756]	Yes [757]	Helicobacter pylori [758], ↓ Bifidobacterium [759]
Small Intestine	Yes [742]		-
Large Intestine	Yes [742]	Yes [760]	Fusobacterium nucleatum, Escherichia coli, Streptococcus bovis, Salmonella enterica, Fusobacterium necrophorum, Porphyromonas gingivalis, Prevotella intermedia [761,762], ↓ Bifidobacterium [759]
Liver	Yes [763,764]	Yes [765,766]	Helicobacter pylori, Enterococcus faecalis [767,768]
Pancreas	Yes [769]	Yes [770]	Fusobacterium nucleatum, Citrobacter freundii, Shigella sonnei, Helicobacter pylori and Porphyromonas gingivalis [771-773], ↓ Bifidobacterium [759]
Kidney	Yes [774]	Yes [775]	-
Uterine Cancer	Yes [776]	-	-

Each of these three systems – the vagus nerve, the microbiome, and the RAS – plays a distinct role in tumor progression, yet they likely interact within a dynamic, interdependent network that regulates the tumor microenvironment. These interactions may either promote or inhibit

tumor progression, depending on the balance of each system. However, it is important to note that the interplay between the vagus nerve, gut microbiota, and RAS is still hypothetical and requires further investigation. These interconnections could reveal a synergistic involvement of the three systems in certain cancers, potentially leading to novel therapeutic possibilities. Comprehensive studies are needed to establish stronger causal links between these systems and tumor progression, particularly by examining how systemic factors, such as nerve activity and immune responses, intersect with localized tumor behaviors. This may lead to more targeted and effective treatments.

6.4 Neuro-circulatory integration in Central Nervous System

All vagal afferents converge at the nucleus tractus solitarii (NTS) [573,777]. The NTS plays a major role in pH regulation [64]. In hypoxia, peripheral chemoreceptors transmit afferent information to the NTS, which then projects to the PVN [677]. In cancer, arcuate nucleus and lateral hypothalamus detect changes in systemic energy balance through peripheral and central chemoreceptors and humoral receptors (which include ligands such as glucose, ghrelin, leptin, and insulin) to normalize peripheral physiology. However, they are unable to do so effectively due to the metabolic and immune continuous stimulus from the tumor [665]. Cytokines are play a major role in signal transmission and are secreted by immune cells (such as macrophages, neutrophils, mast cells, and lymphocytes)**.** The PVN can also receive information via the bloodstream about metabolic/immune stress caused by cancer through pro-inflammatory interleukins (IL-1; IL-6), TNF-α, T-cells, macrophages [665,778,779], and Ang II [780]. Indeed, the PVN is one of the most vascularized regions of the CNS [781]. The NTS and the PVN contains AT1R [729,782]. Vagal afferent fibers modulate the excitability of ANG II- and osmo-sensitive median preoptic neurons (MnPO), altering their input to the PVN [783].

All of the information of section 2 are summarized in Figure 6.1 below:

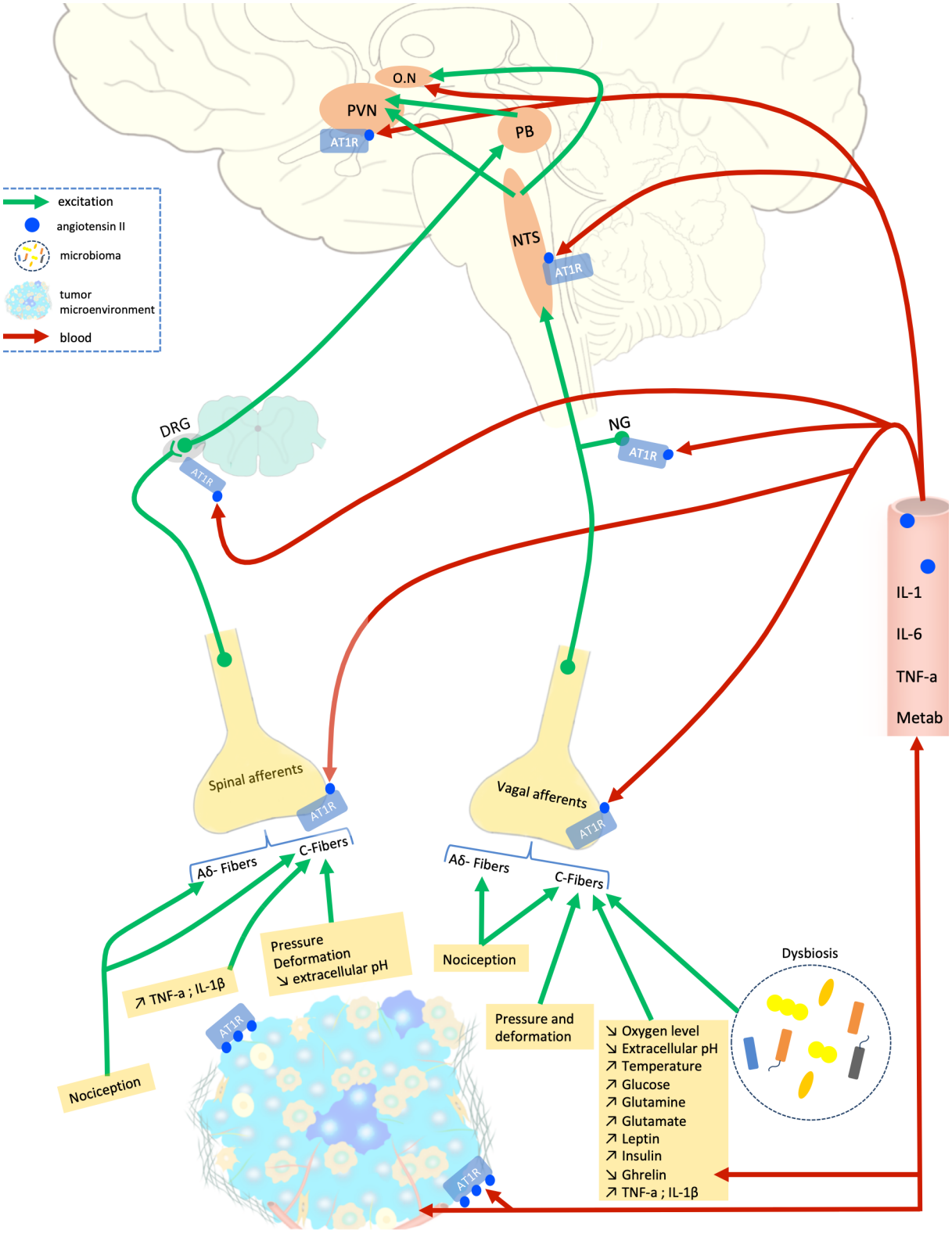

Figure 6.1. Summary of Tumor-CNS Communication via Afferent Sensory Nerve Fibers in Vagal-Innervated Organs.

Spinal afferent nerves generally respond to nociceptive signals related to heat, cold, low pH, as well as mechanoreceptors (pressure/deformation) and inflammatory signals. In contrast, vagus nerve contain a variety of receptors that can respond to a broader range of information related to the tumor microenvironment. This information depends on the tumor's location (see Table 6.1), but generally includes metabolic variations, hypoxia, temperature, pressure changes, inflammation, and the microbiota. Angiotensin II, present in circulation, may bind to angiotensin type 1 receptors (AT1R) located in all the autonomic effector and integrative centers linked to the tumor microenvironment. There are communications between the main centers; for example, the Nucleus Tractus Solitarii (NTS) projects to the arcuate nucleus and the lateral hypothalamus [784,785], and these nuclei project to the ParaVentricular Nucleus of hypothalamus (PVN) [786]. The NTS and PVN contain reciprocal innervations [787]. The parabrachial nucleus functions as a sensory relay, receiving inputs from visceral, nociceptive, and thermoreceptive signals from the periphery and transmitting this information to the hypothalamus and amygdala. Thus, all the information conveyed by circulation and sensory neurons can be transmitted and integrated into the main autonomic regulatory centers, namely the NTS and PVN.
AT1R: Angiotensin Type 1 Receptor; DRG: Dorsal Root Ganglia; IL-1: InterLeukin-1; IL-6: InterLeukin-6; Metab: Metabolites; NG: Nodose Ganglia; NTS: Nucleus Tractus Solitarii; O.N: Other Nuclei of hypothalamus; PB: ParaBrachial; PVN: ParaVentricular Nucleus of hypothalamus; TNF-α: Tumor necrosis factors-alpha.

Thus, in this Section 2, we have aimed to summarize the underexplored role of vagal afferent fibers in the communication between the tumor microenvironment and the CNS. The stimulation of vagal afferent fibers contributes to metabolic dysfunction induced by sympathoexcitation [695] and the reduction of cardiac efferent parasympathetic effects [788]–two mechanisms observed in cancer that we will revisit in Section 3.

6.5 Efferent Central Nervous System-Tumor pathways

6.5.1 Do sympathetic and parasympathetic efferents influence cancer?

Sympathetic fibers

Sympathetic nerves are more frequently found in the tumor microenvironment (TME) and are more involved in the advanced stages of the disease [789,790]. Sympathetic nerves innervating the

tumor microenvironment promote cancer progression and are associated with stress-induced cancer behavior. Regarding angiogenesis, many studies suggest that axons guide, and regulate angiogenesis [791,792], particularly those of the sympathetic system. The sympathetic nervous system is typically regarded as a regulator of the tumor microenvironment, primarily because of its pro-inflammatory effects and its role in driving angiogenesis [792-794]. Axonogenesis and angiogenesis are essential processes for maintaining the tumor environment, cancer progression, metastasis, and ensuring CNS-tumor communication. Locally, in the tumor microenvironment, autonomic fibers innervate stromal cells. The sympathetic nervous system (SNS) is involved in the early [795] and late stages [796] of the disease. Nerve growth factors' (NGFs) have been identified in many different types of cancer [797], as new axons are created from sensory nerves (afferent fibers of the vagus nerve and spinal nerves) [792,798]. Cancer cells have been shown to induce axonogenesis in vitro, suggesting that proNGF/NGF are molecular mediators of tumor axonogenesis in prostate cancer [799] human gastric and colorectal CSCs are capable of producing neurons, particularly autonomic neurons, when they generate tumor masses [800]. Sympathetic nerves and adrenergic signaling, particularly through β2-AR and β3-AR receptors, are involved in tumor angiogenesis. The loss of this signaling leads to reduced blood vessel formation and a halt in tumor growth. Sympathetic fibers thus play a key role in regulating angiogenesis and tumor progression by supporting aerobic glycolysis rather than oxidative phosphorylation [801]. Sympathetic denervation through chemical methods in tumor-bearing mice eliminated the disruptions in glucose metabolism [802].

Parasympathetic fibers

The parasympathetic nervous system (PSNS) plays an intriguing role in the later stages of cancer, showing both pro-tumor and anti-tumor effects depending on the context. Magnon et al. [795] highlight that the PSNS might influence cancer progression, especially in advanced stages.

Pro-tumor Effects

PSNS receptors, such as the type 3 muscarinic acetylcholine receptor, play a role in tumor progression [803-805]. Overexpression of these receptors is linked to glucose dysregulation (related to the Warburg effect) and obesity [806], both critical factors in tumor progression. Activation of this receptor subtype promotes nerve innervation in gastric cancer via NGFs cancer [807]. In gastric cancer, some studies suggest pro-tumor effects of PSNS activity [166]. Similar results have been noted in colon cancer [808]. Vagotomy has been observed to inhibit tumor progression in some cases [166], in murine pancreatic cancer models, vagotomy has been associated with

accelerated tumor progression and reduced survival, mediated by tumor-associated macrophages (TAMs) and TNF-α [809]. Furthermore, vagotomy has been shown to increase NF-κB activation in neutrophils and macrophages, along with elevated levels of IL-1β, IL-6, interferon-γ, and TNF-α, indicating a pro-inflammatory response [810].

Anti-tumor Effects

Conversely, PSNS can exert significant anti-tumor effects under certain conditions. Vagus nerve stimulation has been linked to the release of TFF2 from splenic memory T cells, which suppresses myeloid cell expansion and inhibits cancer progression in colorectal cancer models [811]. The vagus nerve also employs acetylcholine (ACh) as a neurotransmitter, which influences cancer progression by regulating energy metabolism through mitochondrial cristae remodeling [812], a process known to be disrupted in cancers [270]. Fully active efferent vagus nerve C-fibers enhance glucose homeostasis [668], a significant observation given that diabetes and obesity–both risk factors for cancer [813]–amplify the Warburg effect [814]. Notably, electrical stimulation of the efferent abdominal vagus nerve has been shown to reduce blood glucose levels both in vivo [815] and in humans [816]. Additionally, ACh may mitigate Ang II-induced upregulation of AT1 receptor expression [817], and the vagus nerve has demonstrated protective effects against metastasis in some contexts [818,819]. The anti-inflammatory effects of the PSNS are also notable. The vagus nerve exerts these effects by binding to α7nAChR on macrophages and immune cells, activating intracellular pathways that inhibit NF-κB and activate JAK2/STAT3, thereby suppressing pro-inflammatory cytokines. ACh also binds to mitochondrial α7nAChRs, inhibiting mitochondrial DNA release and inflammasome activation [654,820,821].

The presence of parasympathetic nerves within tumors is not consistently confirmed [822,823]. Supradiaphragmatic (+++) and subdiaphragmatic (+) vagal efferent nerves can be inhibited by a tumor's hypoxic environment [824]. Given the dual roles of macrophages–pro-inflammatory (type 1) versus anti-inflammatory (type 2)–cholinergic and adrenergic receptor expression on macrophages appears to vary based on disease stage and tumor microenvironment. This suggests that vagal signaling dynamically influences receptor expression during cancer progression [796,825-829]. In conclusion, the complex and sometimes contradictory findings on the role of the PSNS in cancer progression highlight the need for a deeper understanding of how parasympathetic signaling influences tumor development and metastasis. The evidence for a consistent neural dependency of tumors remains weak [789,790,793].

6.5.2 Systemic inhibition of vagal efferent fibers in tumors in vagal-innervated organs?

Heart rate variability and inflammation

De Couck et colleagues hypothesize that a high CVT may inhibit three key oncogenic mechanisms: oxidative stress, inflammation, and excessive sympathetic activity [17]. Vagal tone (cardiac efferent) can be measured using a method called HRV. HRV is an easy non-invasive measurement that indicates the time variations between two consecutive heartbeats, reflecting the state of the autonomic nervous system [476]. The HRV is generated by sinus node and is mediated by vagal B fibers of nA [830]. Overall, CVT is very low, and the sympathetic-parasympathetic balance is disrupted in cancer patients [24]. Indeed, HRV has been shown to be a reliable prognostic factor for survival in several studies [17,23]. The shorter the time between two consecutive heartbeats, the less variability the heart has, indicating sympathetic dominance and thus a lower HRV. Therefore, CVT is very low in many types of cancer (prostate, pancreatic, gastrointestinal, genitourinary, respiratory, breast), regardless of their location in trunk [78,831]. The markers of HRV are similar in non-solid cancers, such as leukemias [82]. A reduction in HRV is directly correlated with cancer stage, where higher grades are associated with lower markers of CVT and autonomic balance, while heart rate (HR) increases with advancing grade [831]. Resting HR, another marker of CVT, is also a predictor of survival. Patients with a lower heart rate tend to have better survival outcomes [832]. It has also been shown that standard therapies reduce vagal tone and sympathetic-parasympathetic balance [109-111], likely due to the inflammation they cause. Thus, the decrease of HRV can be caused by increased SNS activity. Indeed, there is an inverse correlation between vagal tone and C-reactive protein (CRP), the main marker of inflammation [833]. Under normal conditions, when vagal tone is high, efferent vagal fibers can significantly decrease NF-κB activation, primarily through ACh, and lower circulating levels of pro-inflammatory cytokines [834]. Thus, its regulatory effects on pro-inflammatory cytokines via nicotinic receptors (α7-nAChR) of acetylcholine in immune cells [668,835], and its ability to enhance mitochondrial dynamics [836,837] are not observed in cancer. Additionally, a low sympathomimetic-vagal balance is mainly associated with elevated levels of IL-6, IL-8, IL-18, NF-κB, and Activator Protein 1 (AP-1), while INF-γ and CTRA exhibit mixed effects depending on the inflammatory and antiviral context [838]. The pro-inflammatory markers mentioned, such as the neutrophil-to-lymphocyte ratio (NLR), systemic inflammatory index (SII), platelet-to-lymphocyte ratio (PLR), fractalkine, soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1), TNF-α, IL-6, IL-1, and CRP, are often associated

with reduced vagal activity, indicating an autonomic imbalance with sympathetic predominance [839].

A study demonstrated that the stimulation of vagal afferent fibers reduced the activity of efferent fibers [788]. These effects could potentially be similar in the context of cancer.

Microbiome

Reduced vagal tone can impair its ability to detect microbiome metabolites through its afferents and to transfer this intestinal information to the CNS. This can happen also through its efferents (by DMNV) by modulating the gut microbiome via changes in intestinal permeability and local immunity [716,840,841]. Vagal stimulation reduced paracellular permeability of the small intestine [842] and restore microbiome in duodenum [843]. Stimulation of the vagus nerve restored the reduced expression levels of tight junction proteins, such as occludin and zonula occludens 1, and preserved their proper localization. Additionally, the vagus nerve stimulation suppressed NF-κB activity within the intestinal mucosa, thereby reducing elevated myosin light chain kinase in endotoxemia, which helps prevent the disruption of tight junctions and protects gut barrier integrity [844].

Renin-angiotensin system

Ang II can inhibit cardiac vagal efferent activity [845,846], in contrast vagus nerve stimulation can inhibit renin [847,848], ang II [849] and reduce expression of AT1R [850].

In summary, in tumors in vagal-innervated organs , the vagus nerve is likely to be predominantly inhibited (see figure 6.2):

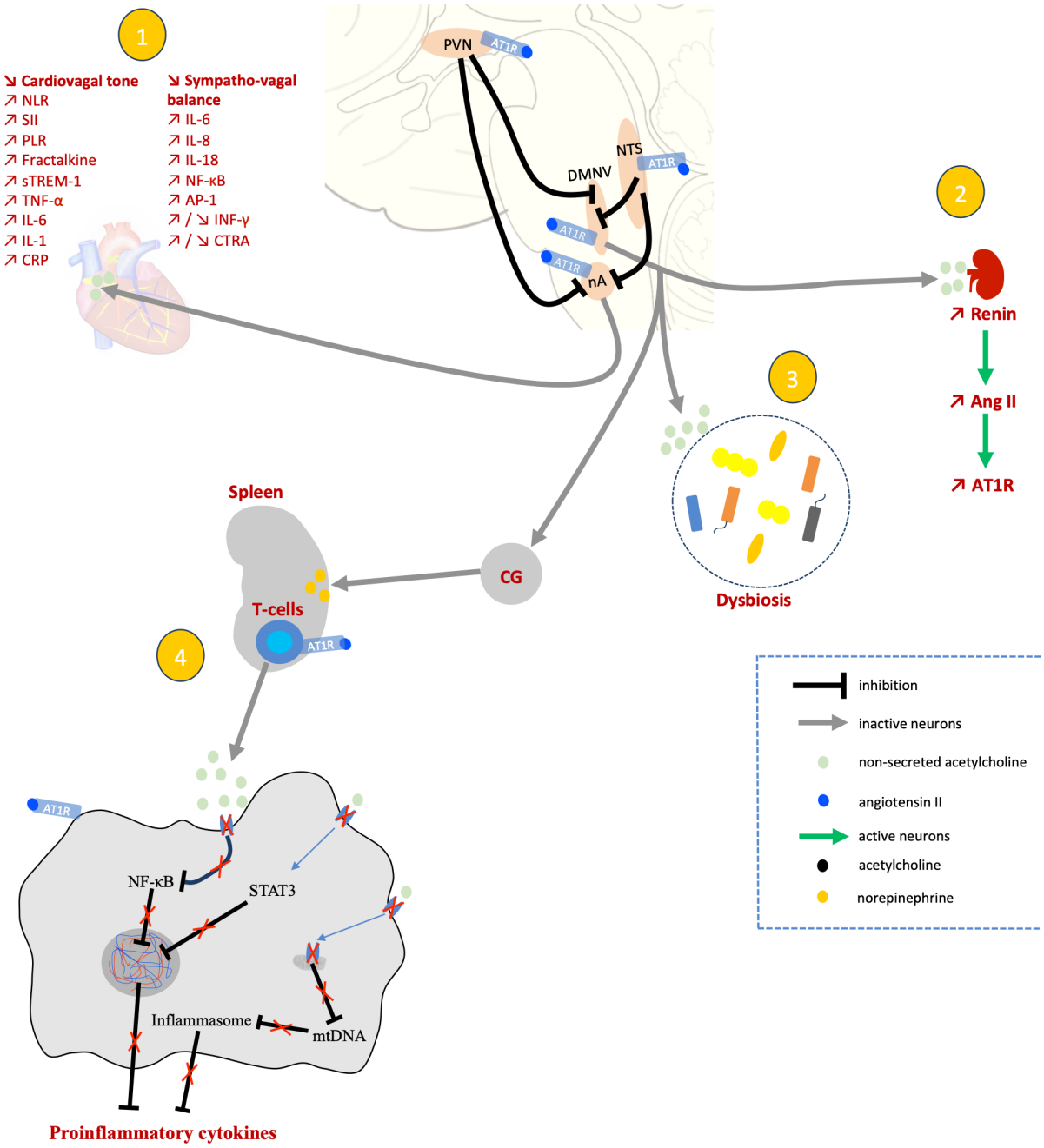

Figure 6.2. Systemic inhibition of vagal efferent fibers in tumors in vagal-innervated organs. *Systemic inhibition of the vagus nerve will result in (1) a reduction in cardiac vagal tone and an increase in CRP; (2) an increase in renin levels, Ang II and AT1R; (3) changes in intestinal permeability and local immunity, leading to dysbiosis; and finally, (4) an increase in pro-inflammatory cytokines by immune cells. Ang II: Angiotensin II; AP-1 : Activator Protein 1; AT1R: Angiotensin Type 1 Receptor; CG: Celiac Ganglia; CRP : C-reactive protein; DMNV: Dorsal Motor Nucleus of the Vagus; mtDNA: mitochondrial DNA; nA: nucleus Ambiguus; NF-κB: Nuclear Factor-kappa B; NTS: Nucleus Tractus Solitarii; PLR : Platelet-to-lymphocyte ratio; PVN: ParaVentricular Nucleus of hypothalamus; SII : Systemic inflammatory index;*

sTREM-1 : soluble Triggering Receptor Expressed on Myeloid cells-1; STAT3: Signal Transducer and Activator of Transcription 3.

6.5.3 Chronic cancer stress engages sympathetic and neuro-immuno-endocrine pathways, impacting various other physiological systems

Two pathways are involved in the chronic stress observed in cancer patients, the SNS pathway secretes norepinephrine and neuropeptide Y, and the HPA axis secretes glucocorticoids/epinephrine. These hormones increase the levels of M2 macrophages involved in metastasis, angiogenesis, and cell proliferation [851]. The SNS and innate immunity do not seem to be "inherently favorable" or "opposed" to the tumor [852]. It could be an adaptive and defensive response of the body. The continuous signals sent by the tumor to the CNS are perceived as stress by the body, which then activates the hypothalamic-pituitary-adrenal (HPA) axis. Given the constant stimuli, the body adopts adaptive mechanisms such as excessive sympathetic activity and chronic inflammation [853]. For instance, chronic inflammation resulting from obesity can influence the PVN (e.g., leptin and insulin resistance) [854], thereby increasing cancer risk [690].

The SNS can act on blood vessels and macrophages to promote tumor progression and metastasis [794]. The activation of the HPA axis, increased SNS activity, and immune modifications are pro-inflammatory and pro-angiogenic phenomena that assist the tumor [855]. The PVN also plays an important role as a mediator in transitioning autonomic information from the cortico-limbic pathways to the brainstem and spinal cord [784,856], influencing HR and HRV [857,858]. The PVN projects neurons to the nA and to the dorsal motor nucleus of the vagus (DMNV)[859] exactly as the NTS [660]. All these centers – nA, DMNV, NTS, and RVLM – contain also AT1R receptors [729,860]. Indeed, RAS works closely with the SNS, often having similar effects and interacting reciprocally to influence each other [861-863]. The PVN regulates vasopressin (VP) which is produced by the magnocellular neurons (MCNs) [864], and circulating vasopressin could regulate RAS by renin secretion [865,866]. Ang II may bind to AT1R in the PVN, thereby increasing sympathetic activity [782,867]. It also plays a major role in osmotic homeostasis via vasopressin [864] and in the control of hypoxia [868].

In turn, the cortico-limbic system affects heart rate HR and HRV through the NTS and PVN [869]. Some cortical and subcortical structures play a role in initiating integrated autonomic responses [777] which can affect HR and HRV. The PVN plays a key mediating role in the transmission of

autonomic information from cortico-limbic pathways (including the medial prefrontal cortex, anterior cingulate cortex, central amygdala, and insula) to the brainstem Research of Dampney and Schaeuble aligns with the mechanisms of cardiac autonomic regulation in response to emotions and stress, as proposed by Thayer [857] and Gianaros [858]. The influence of the limbic system on the regulation of autonomic centers may partially explain the benefits of psychosocial interventions for cancer patients, contributing to improved survival outcomes [870].

All the cortical structures involved in stress related to cancer progression are summarized in figure 6.3 below:

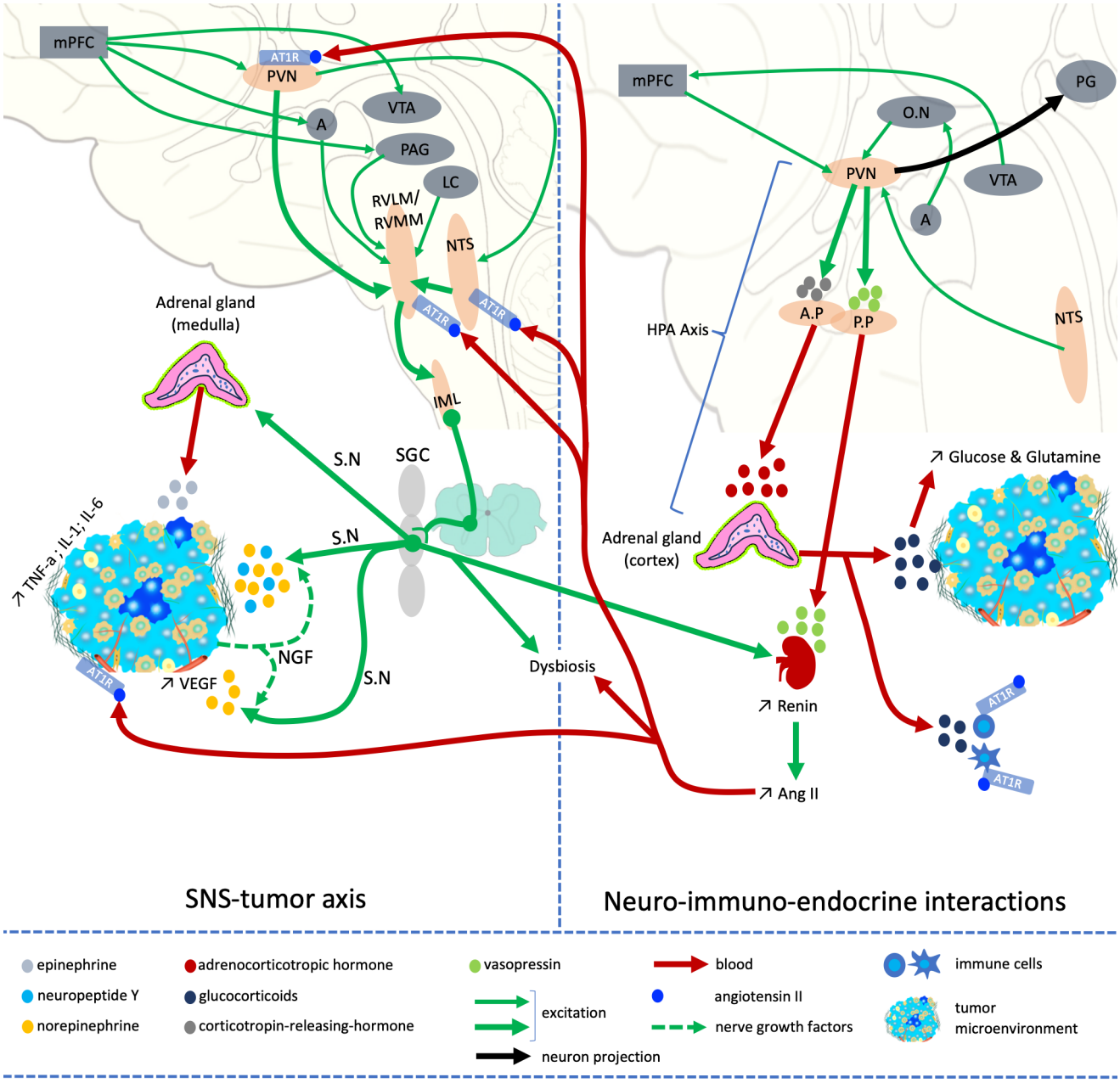

Figure 6.3. A comprehensive summary of efferent pathways involving the central nervous system and tumors.

In the left panel, the interactions related to the sympathetic-stress-tumor axis are summarized. The small green excitatory arrows represent the interactions, particularly from the cortico-limbic centers to the integrative and autonomic regulatory centers. The large green arrows from the paraventricular nucleus of the hypothalamus (PVN) and the nucleus of the solitary tract (NTS) represent the projections from the integrative and regulatory centers to the sympathetic premotor regions, the rostral ventrolateral medulla (RVLM) and the rostral ventromedial medulla (RVMM). In turn, the RVLM and RVMM project excitatory neurons to the spinal cord and the sympathetic nerves (SNS). Some sympathetic nerves project to the adrenal medulla, leading to the release of epinephrine into the circulatory system, while others release norepinephrine and neuropeptide Y into the tumor and its microenvironment. The tumor itself can produce nerve growth factors that allow sympathetic nerves to sustain the tumor's microenvironment, essential for its growth.

In the right panel, the neuro-immuno-endocrine-tumor axis interactions are summarized. The small green excitatory arrows represent the interactions, especially from cortico-limbic centers to the integrative and autonomic regulatory centers. The PVN and NTS receive projections from various hypothalamic centers involved in the regulation of stress and neuroendocrine functions, such as the Arcuate Nucleus and the Lateral Hypothalamus [854,871]. The PVN acts as the key orchestrator of this axis, releasing adrenocorticotropic hormone (ACTH) to the anterior pituitary gland, which in turn secretes corticotropin-releasing hormone (CRH) into the bloodstream, leading to the release of glucocorticoids from the adrenal cortex. Glucocorticoids act on the tumor microenvironment, causing immunosuppression [872], increasing also glucose levels [873] and glutamine metabolism [874]. The PVN also releases vasopressin into the posterior pituitary, which then releases vasopressin into the bloodstream, increasing renin levels and thus circulating Ang II. There appears to be a self-amplifying loop between the sympathetic-stress axis and the neuro-immuno-endocrine axis, as Ang II can bind to AT1R in the PVN and increase sympathetic output [875]. The sympathetic nervous system itself can enhance renin secretion and Ang II levels [876]. Ang II also promotes dysbiosis [747], similar to the sympathetic nervous system [877,878]. Finally, adrenergic neurons in the PVN regulate melatonin secretion by the pineal gland, with melatonin exhibiting anticancer effects [879]. The figures were partially inspired by several references [635,859,880].

A: Amygdala; AT1R: Angiotensin Type 1 Receptor; DRG: Dorsal Root Ganglia; HPA: Hypothalamic–Pituitary–Adrenal; IL-1: InterLeukin-1; IL-6: InterLeukin-6; IML: InterMedioLateral cell column; mPFC: medial PreFrontal Cortex; NG: Nodose Ganglia; NGF: Nerve Growth Factor; NTS: Nucleus Tractus Solitarii; O.N: Other Nuclei of

hypothalamus; PAG: PeriAqueductal Gray; PB: ParaBrachial; PG: Pineal Gland; PVN: ParaVentricular Nucleus of hypothalamus; RVLM: Rostral VentroLateral Medulla; SGC: Sympathic Ganglia Chain; S.N: Sympathetic Nerve; TNF- α: Tumor necrosis factors-alpha; VEGF: Vascular endothelial Growth Factor, VTA : Ventral Tegmental Area

The different pathways of chronic cancer stress are involved in tumor development and metastasis through their pro-inflammatory and pro-angiogenic actions.

6.6 Current Experimental Approaches: Limitations and Future Directions

Recent controversies regarding the rigor of studies on tumor progression and the role of the vagus nerve [638], underscore a major methodological challenge in understanding the underlying mechanisms. Numerous factors may account for the discordant findings observed in the interaction between the vagus nerve and cancer progression, whether at the local or systemic level.

A major limitation of current studies is their tendency to extrapolate local effects observed in tissues to systemic effects, without adequately considering the complexity of the tumor microenvironment. These apparent contradictions between the local and systemic roles of the vagus nerve highlight the need for experimental approaches capable of capturing the complexity of neuro-oncological interactions. For instance, studies have demonstrated that sensory nerve activity, including that of the vagus nerve, can modulate metastatic dissemination without significantly affecting primary tumor growth [666]. Conversely, local effects can vary significantly depending on the heterogeneity of sensory nerve fibers at a specific site and the diversity of other neuronal and immunological factors within the tumor microenvironment. This suggests that local and systemic mechanisms may differentially influence tumor progression, an aspect often underestimated in current research.

Moreover, traditional experimental approaches, such as vagotomy, suffer from a critical limitation as they fail to clearly distinguish the contributions of afferent and efferent vagal fibers. This complicates the interpretation of results and impedes a clear understanding of the pro- or antitumoral effects of vagal signaling. Technological advances, such as optogenetic or chemogenetic manipulation of specific nerve fiber subpopulations, could help isolate the contributions of afferents and efferents in the tumor context more precisely.

The diversity of vagus nerve receptors, capable of detecting changes in the tumor microenvironment, could also play a key role in transmitting information between tumors it directly innervates and the central nervous system. However, while these hypotheses are

promising, they require validation through high-resolution molecular studies, such as single-cell RNA sequencing of vagal fibers innervating tumor tissues. These approaches could clarify how specific receptors, such as TRPA1, GPR65, or Oxtr+, influence tumor behavior and systemic signaling.

Finally, the interactions between the vagus nerve, gut microbiome, and the RAS may play a role in tumor progression. To validate these links, metabolic and transcriptomic approaches combined with in vivo imaging techniques are needed.

6.7 Conclusions and perspectives

This review highlights the underexplored role of the vagus nerve in the interactions between the tumor microenvironment and the central nervous system (CNS). Through its distinctive receptor profile, the vagus nerve could have the potential to relay critical immune, metabolic, mechanical, and chemical signals from tumors to the CNS, thereby influencing cancer progression in ways that remain to be fully elucidated. Moreover, its interactions with other key systems, such as the microbiota and the renin-angiotensin system (RAS), could further strengthen its potential central role in modulating tumor-related responses, though these connections remain largely underexplored. From a therapeutic perspective, several innovative approaches could potentially emerge, although they would still be in the early stages of exploration. The targeted modulation of vagal afferent fibers might, for instance, be achieved through the blockade of specific metabolic receptors like Glucagon-Like Peptide-1 or 5-hydroxytryptamine 3 receptors, which could potentially limit tumor-CNS communication and reduce pro-inflammatory responses that may promote tumor progression. Another promising strategy could involve modulating integrative autonomic centers, such as the paraventricular nucleus (PVN) of the hypothalamus, through techniques like optogenetics or by targeting the angiotensin II type 1 receptor (AT1R). Finally, combined approaches–including the systemic stimulation of vagal efferent fibers, administration of probiotics, and the use of AT1R inhibitors (e.g., sartans)–might help regulate inflammatory pathways, suppress tumor growth, and reduce metastatic risks. Advancing our understanding of the neuro-oncological mechanisms underlying the role of the vagus nerve would be essential to fully realize the potential of novel therapeutic strategies based on autonomic pathway modulation.

Chapter 6 reveals that the systemic inhibition of vagal efferent activity in vagally-innervated cancers is not an isolated phenomenon – it is part of a broader metabolic and neuro-immune dysregulation that sustains tumor growth. Among the systemic consequences of this

dysregulation, hyperglycemia occupies a central place: glucose is both an essential fuel for cancer cells and a direct product of the treatment-induced stress response. Chapter 7 quantifies this risk through a systematic review and meta-analysis, confirming that standard oncological treatments consistently elevate blood glucose – and that this elevation is clinically significant across nearly all cancer types.

7. Chapter 7: Cancer treatment and glycemic outcomes: a systematic review and meta-analysis.

Submitted in Cancer Control the May 14, 2026.

General abstract and Key Points of the Article:

This article presents a systematic review and meta-analysis investigating the impact of standard cancer treatments on glycemic control. The primary objective was to determine whether cancer patients are at increased risk of treatment-induced hyperglycemia, whether transient or persistent, and, if so, to propose recommendations for glycemic management in this population. The metabolic framework established in Chapter 4 identified glucose as an essential and sufficient fuel for cancer cells, while Chapter 6 demonstrated that impaired vagal efferent activity can disrupt glycemic regulation through cholinergic pathways. These findings raise both a clinical and mechanistic question: to what extent do standard oncological treatments exacerbate this metabolic vulnerability by increasing blood glucose levels? Chapter 7 addresses this question directly, thereby closing the loop between vagal dysregulation, tumor metabolism, and therapeutic practice.

Abstract

Objectives:

Hyperglycemia is a common metabolic complication in cancer patients, often induced as a side effect of cancer treatments. This study aims to summarize the impact of standard cancer treatments on glycemia in cancer patients.

Methods:

We searched PubMed (MEDLINE), Embase, ScienceDirect, and the Cochrane Library, with a search cutoff of September 12, 2025. Eligible studies, including randomized controlled trials, cohort, and observational studies, focused on treatment-induced hyperglycemia and diabetes in cancer patients, following PRISMA guidelines. Data extraction was based on the PICO

framework, with overall prevalences estimated using the Freeman-Tukey (arcsine) transformation. The study was registered with PROSPERO (CRD420251026027) and analyzed using a random-effects meta-analysis, considering cancer type, treatment regimen, and follow-up duration.

Results:

A total of 91 articles met the inclusion criteria, involving 238,451 patients (41.9% men, 56% women). The post-treatment prevalence of hyperglycemia was 26%, while type 2 diabetes prevalence was 10.6%. A meta-analysis of 28 studies (54,659 patients) revealed a statistically significant effect of treatment-induced hyperglycemia (θ_{RE}=0.7230, CI_{95}=[0.6133-0.8326]). Inter-study variance (τ) was (τ=0.2840)**,** reflecting moderate variability. Subgroup analyses showed significant effects across treatment types, with variation by corticosteroid use, combination therapies, and follow-up periods.

Conclusions:

This systematic review and meta-analysis demonstrates the necessity of considering hyperglycemia and/or type 2 diabetes in patients with cancer. Recommendations are proposed to improve glycemic management in cancer patients.

Keywords: Glycemia, Hyperglycemia, Prediabetes, Diabetes, Cancer, Standard care, Metabolism.

7.1 Introduction

Cancer is a complex disease that continues to drive a steady increase in mortality worldwide, with an estimated 19.3 million new cases and 10 million deaths reported annually [881]. According to recent data from the American Cancer Society, more than 618,000 people in the United States are expected to die from cancer this year [882]. A study conducted on 722,532 individuals found that the rising rates of diabetes and prediabetes in the U.S. are associated with an increased cancer risk [883]. The study shows a statistically significant link between diabetes/prediabetes and cancer, with factors such as obesity, insulin resistance, and hyperglycemia potentially playing a role in this association. Cancer cells require energy, and glucose, as a fermentable fuel and biosynthetic, is both essential and sufficient to sustain their growth [884–886]. It is well established that certain treatments, such as corticosteroids can increase blood glucose levels [887, 888].

Moreover, corticosteroid-induced hyperglycemia seems to be largely unpredictable in cancer patients [889]. Emerging evidence further suggests that therapy-induced hyperglycemia is not only associated with an increased risk of metabolic toxicity [890], but also with a higher likelihood of exacerbating type 2 diabetes risk in cancer patients, particularly with androgen deprivation therapy (ADT) [891]. Furthermore, standard systemic oncology therapies have been shown to contribute to this heightened risk [892]. Hyperglycemia post-surgery is associated with increase infection and increase-risk of mortality [893, 894].

Only some metabolic consequences of some therapies on glycemia are known. The impact of all possible cytotoxic and medical therapies or combined regimens remains underestimated and insufficiently explored. Experimental in vitro and in vivo data on chemotherapy further highlight that hyperglycemia can impair treatment effectiveness [895].

Conventional cancer care is administered with the intention of eliminating tumor cells or slowing down their replication. However, therapy-induced hyperglycemia is not without risks for cancer patients, which could be prevented or mitigated with pro-active management. Indeed, several studies have reported that hyperglycemia and type 2 diabetes in cancer patients are associated with lower survival (see Table 1 below).

Table 7.1. Risk of mortality of major cancer related to hyperglycemia

Source	Patients (n)	Study type	Cancer/Disease	Main findings
Barua R et al.[896]	9 872	Systematic review & Meta-analysis	Solid tumors (Glioblastoma, Non-small cell lung, Pancreatic, Breast, Hepatocellular carcinoma, Gastric, Cervical, Esophageal)	Hyperglycaemia was associated with worse overall survival (hazard ratio 2.05, CI_{95}=[1.67–2.51]; p<0.001) and DFS (HR=1.98, CI_{95}=[1.20–3.27]; p=0.007), but did not affect PFS (HR=1.08, CI_{95}=[0.72–1.62]; p=0.71).
Barami K et al.[897]	1 144	Systematic review	Glioblastoma	Among various metabolic factors studied in GBM, hyperglycemia was the most consistently associated with decreased survival (8/12 studies), whereas T2DM, obesity, corticosteroid, and metformin use showed variable effects.
Liu H et al.[898]	2 168	Systematic review & Meta-analysis	Glioblastoma	Hyperglycemia predicted shorter survival in brain tumors (HR=2.04, CI_{95}=[1.51–2.76]), confirmed across sub-analyses (HR=1.82, CI_{95}=[1.29-2.59]). Diabetes was also associated with poor survival (HR=2.09, CI_{95}=[1.22-3.57]). No difference was observed between corticosteroid- and diabetes-induced hyperglycemia.
Xu W et al.[899]	21 871	Systematic review & Meta-analysis	Oral & Oropharyngeal cancer	Diabetes associated with poor OS (HR=1.69) and PFS (HR=1.61). Stronger effect in patients ≥52 years compared to those aged <52 years (HR=2.08 vs 1.34).

Source	Patients (n)	Study type	Cancer/Disease	Main findings
Zhang D et al.[900]	17 451	Systematic review & Meta-analysis	Ovarian cancer	Diabetes (especially T2DM) associated with 40–50% increased risk of all-cause and cancer-specific mortality.
Cai H et al.[901]	≈ 218 492	Systematic review & Meta-analysis	Prostate cancer	Diabetes in prostate cancer patients is associated with increased risk of mortality: all-cause (HR=1.50), prostate cancer-specific (HR=1.26), and non-prostate cancer mortality (HR=1.83).
Chen S et al.[902]	11 091	Systematic review & Meta-analysis	Cervical cancer	Diabetes independently associated with poor OS (HR=1.69) and RFS (HR=1.98
Deng HY et al.[903]	4 343	Systematic review & Meta-analysis	Non-small cell lung cancer	Diabetes associated with poorer OS (HR=1.30, CI_{95}=[1.05–1.60]), but not with RFS (HR=1.06, CI_{95}=[0.71–1.58]) after surgical resection of NSCLC.
Jing C et al.[904]	5 522 636	Systematic review & Meta-analysis	Gallbladder cancer	Diabetes is associated with increased gallbladder cancer mortality (HR=1.10, CI_{95}=[1.06–1.14]). No significant sex differences were observed.
Mao Y et al.[905]	19 818	Systematic review & Meta-analysis	Pancreatic cancer	Diabetes associated with poor survival in resec Nuclear Genetic Mutation disease (HR=1.37) and new-onset diabetes (HR=1.52), but not significant in unresectable disease.

Notes. CI_{95}: Confidence Interval at 95%; DFS: Disease-Free Survival; GBM: Glioblastoma Multiforme; HR: Hazard Ratio; NSCLC: Non-Small Cell Lung Cancer; OS: Overall Survival; PFS: Progression-Free Survival; RFS: Recurrence-Free Survival; T2DM: Type 2 Diabetes Mellitus.

Taking these factors into account, and to fill the gaps in current research, this systematic review and meta-analysis aims to assess whether cancer patients experience significant variations in blood glucose levels as a result of standard treatments, either as monotherapy or in combination. These variations, both in the short and medium term, remain insufficiently characterized, despite the growing evidence linking hyperglycemia, hyperinsulinemia and its associated risks, to common oncological therapies. Our objective is to provide a clearer understanding of the impact of these treatments on glycemic control, which could inform better management strategies for cancer patients.

7.2 Research design and methods

Search Strategy and Inclusion Criteria

The eligibility criteria, outcomes, main, and moderator analyses were pre-specified and published in PROSPERO (April 2025, CRD420251026027). We followed the Preferred

Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [906]. A systematic search was conducted on Science direct, PubMed, the Cochrane Library database for articles published until September 12, 2025. A snowball procedure completed the research. The following search terms were used on Pubmed: (cancer surgery) AND (hyperglycemia[MeSH Terms]); (cancer surgery) AND (type 2 diabetes mellitus[MeSH Terms]); (cancer surgery) AND (blood glucose[MeSH Terms]); (cancer surgery) AND ("Postoperative Period"[MeSH]) AND (type 2 diabetes mellitus[MeSH]); (cancer surgery) AND ("Postoperative Period"[MeSH]) AND (blood glucose[MeSH]); (cancer surgery) AND ("Postoperative Period"[MeSH]) AND ("Hyperglycemia"[MeSH]); (antineoplastic agents[MeSH Terms]) AND (blood glucose[MeSH Terms]); (antineoplastic agents[MeSH Terms]) AND (hyperglycemia[MeSH Terms]); (antineoplastic agents[MeSH Terms]) AND (type 2 diabetes mellitus[MeSH Terms]); (chemotherapy) AND (hyperglycemia[MeSH Terms]); (radiotherapy) AND (blood glucose[MeSH Terms]); (radiotherapy) AND (diabetes[MeSH Terms]); (radiotherapy) AND (hyperglycemia[MeSH Terms]); ((oncology) AND (steroids[MeSH Terms])) AND (hyperglycemia[MeSH Terms]); ((oncology) AND (steroids[MeSH Terms])) AND (diabetes[MeSH Terms]); ((oncology) AND (steroids[MeSH Terms])) AND (blood glucose[MeSH Terms]); (immunotherapy) AND (hyperglycemia[MeSH Terms]); (immunotherapy) AND (type 2 diabetes mellitus[MeSH Terms]); (immunotherapy) AND (blood glucose[MeSH Terms]).

The following search terms were used on Science Direct: “surgery” AND “hyperglycemia” AND “cancer”; “chemotherapy” AND “hyperglycemia” AND “cancer”; “radiotherapy” AND “hyperglycemia” AND “cancer”; “corticosteroids” AND “hyperglycemia” AND “cancer”; “immunotherapy” AND “hyperglycemia” AND “cancer”; “antineoplastic agents” AND “hyperglycemia” AND “cancer”. We only selected articles categorized as “Research Articles”. The following search terms were used for Cochrane library: “cancer” and “surgery” and “hyperglycemia”; “hyperglycemia” and “chemotherapy”; “hyperglycemia" and “radiotherapy”; ”corticosteroids” and “hyperglycemia”; and “antineoplastic agents” and “hyperglycemia” and “cancer”. The reference lists of identified articles were then manually searched to identify potentially relevant omitted citations. Articles that were not published in English were not included.

Retrospective and observational studies (i.e., cohort studies, excluding case reports and case series) as well as prospective trials were eligible if they reported an association between

conventional cancer treatments and the incidence of treatment-induced hyperglycemia and/or diabetes. Eligible studies were restricted to follow-up (long-term) periods of up to 5 years during and after treatment, corresponding to the reference window most frequently used to assess survival and recurrence. Accordingly, studies assessing long-term outcomes in cancer survivors beyond 5 years were excluded. In addition, studies related to surgeries in cancer patients that included glucose infusion (or it's derivates as dextrose) were excluded. All studies that included any methods of hyperglycemia or diabetes prevention were excluded, unless they included a comparative group without these management strategies. Studies were also excluded when the diabetes could have been disease-induced rather than treatment-induced, as can sometimes occur in pancreatic cancer. No restrictions were applied regarding study setting, patient age, sample size, race, country, tumor type, or tumor site. Studies including patients with type 1 diabetes or central diabetes insipidus were excluded. All grades of hyperglycemia were considered and included in the percentages of induced hyperglycemias.

For each study, the most recent and complete version of the full-text publication was considered. The selection process was conducted in two phases: initial screening of titles and abstracts, followed by a full-text review based on predefined eligibility criteria. In cases where pooled analyses or meta-analyses were considered, individual articles were manually assessed to avoid duplicate inclusion with other eligible studies. All steps of the process were cross-validated by at least two reviewers.

Data Collection and Quality Assessment

Data were collected independently by using a predesigned spreadsheet (Excel, Microsoft 365, Microsoft Corp). Extracted data items included: reference, number of patients, age, sex, study design, country, disease, baseline glycemic status before treatment, median follow-up, treatment of interest, concomitant treatments, dosage, type of analysis, percentage of hyperglycemia, percentage of treatment-induced diabetes, glycemic assessment criteria, glucose-related adverse events, and study quality. The primary outcome was the number of hyperglycemia events; secondary endpoints included the value of hyperglycemia, the number of treatment-induced diabetes, type of treatment received, and dosage. Study quality was independently assessed by two authors (P.M. and N.Q.) using a modified Newcastle Ottawa Scale [907], ROBINS-I [908], and ROB 2 [909].

Statistical Analysis

A meta-analysis was conducted to estimate the overall prevalence of hyperglycaemia using a proportions-based approach with the Freeman-Tukey double arcsine transformation.[910] This transformation was applied to stabilize variances, improve the symmetry of the distribution of proportions, and permit the inclusion of studies reporting zero events. The Freeman–Tukey transformation was preferred over logit-based approaches because of the high frequency of studies with zero events[911].

In the absence of individual-level paired contingency tables, independence between pre-treatment and post-treatment proportions was assumed. For each study, effect sizes were defined as the difference between the Freeman–Tukey–transformed proportions of hyperglycaemia after and before treatment. This assumption may lead to conservative variance estimates and should be considered when interpreting pooled effects.

The variance of each transformed difference was approximated as 1/(2N), in accordance with variance-stabilizing properties of the Freeman-Tukey transformation. Study-specific effect estimates and their 95% confidence intervals were displayed using forest plots.

Pooled effects estimates were calculated using a random-effects model based with between-study variance estimated by the DerSimonian–Laird method[912] and are reported with corresponding 95 % Confidence Intervals (CIs).

Statistical heterogeneity was assessed using the I^2 statistic and Cochrane's Q under the fixed-effect assumption, and by τ^2 under the random-effects model. I^2 values were interpreted as follows: 0–25% (low), 25-50% (moderate), 50-75% (high), and 75–100% (extremely high heterogeneity). τ values were interpreted as <0.2 (low), 0.20 to 0.40 (moderate), and >0.40 (high between-study variance).

Prespecified subgroup analyses were performed to explore potential sources of heterogeneity, including pre-existing diabetes status, exposure to corticosteroids, treatment strategy (monotherapy versus combination therapies), and follow-up duration.

7.3 Results

Our literature search yielded 26,737 articles, of which 91 (0.34%) met the inclusion criteria for our overall systematic review of the treatment-associated hyperglycemia during cancer therapies (Figure 1). Most of the studies excluded from the eligible studies concerned in vitro

studies or case reports (n = 223) or studies with out of inclusion criteria (n = 133, lack of data on blood glucose levels before and/or after, studies where the blood glucose follow-up exceeded the inclusion criteria).

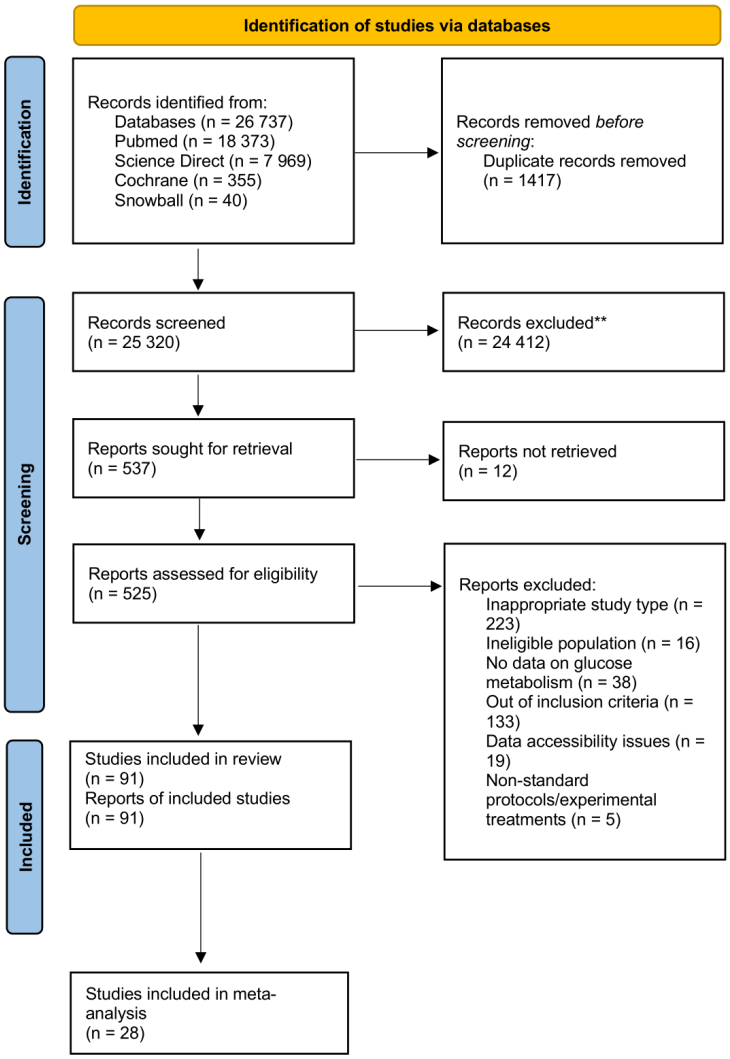

Figure 7.1. Prisma flow diagram of included studies.

Descriptive data for studies included in our meta-analysis are listed in Table 2. Overall, the studies include a total of 238,451 patients, consisting of 99,955 men (41.9%), 133,440 women (56%), and 5,056 individuals (2.1%) whose gender was not specified. Sample sizes ranged from 16 to 74,526 patients, with a median of 155. The study includes various types of cancer, namely: Brain, Breast, Colorectal, Endometrial, Head & Neck, Leukemia, Lung, Lymphoma, Melanoma, Myeloma, Ovarian, Pancreas, Prostate, Various Cancers (studies including a mix of different cancer types). The most numerous studies by cancer type are: Various (23 studies), Leukemia (16 studies), Breast (14 studies), and Brain (11 studies). Most studies were

retrospective cohort (72 studies [80%]), 13 prospective trials, 3 non-randomized controlled trials, and 2 randomized controlled trials. The qualitative assessment of the articles revealed NOS Scale ratings ranging from 1 to 9. The evaluation of randomized indicated a low risk of bias for one study, while the other exhibited a high risk of bias. The non-randomized studies indicated serious risk of bias. All raw data are available in the Supplementary Material 1.

Table 7.2. Characteristics of included studies in systematic review

Ref	N	N(aft)	Age (years ± sd/range)	M/F	Type	Local	PDb-BF	Db-BF	NM Gl-BF	Follow-up	TTT	HGl-AFT	Quality
Chaichana et al. [913]	182	182	36±15	107/75	R	Brain	NA	7	175	1 to 3 months	Surgery, corticosteroids, radiotherapy and chemotherapy	18	NOS: 6/9
McGirt et al.[914]	367	367	54±13	NS	R	Brain	NA	17	350	1 to 3 months	Surgery, corticosteroids, chemotherapy	96	NOS: 6/9
Link et al.[915]	157	157	54±17	88/69	R	Brain	NA	12	145	4-day after surgery	Surgery and corticosteroids	16	NOS: 7/9
Decker et al.[916]	108	108	60.5	61/47	R	Brain	NA	20	88	2-day after surgery	Surgery and corticosteroids	32	NOS: 8/9
Duma et al.[917]	37	37	64.3 (27.4–85.6)	15/22	R	Brain	NA	8	29	Likely 6–8 weeks	Radiotherapy and corticosteroids	21	NOS: 3/9
Adeberg et al.[918]	262	262	63.2 (19.9–82.9)	163/99	R	Brain	NA	32	230	6 weeks	Chemotherapy, radiotherapy and corticosteroids	125	NOS: 5/9
Jatana et al.[919]	199	147	63±11	119/80	R	Brain	NA	31	168	7 days	Surgery and Corticosteroids	105	NOS: 8/9
Pantelidis et al.[920]	56	56	64.0	35/21	R	Brain	NA	21	35	7 days	Surgery, corticosteroids, antihyperglycemic agents, and insulin	15	NOS: 7/9
Welch et al.[921]	988	988	66	NS	R	Brain	NA	89	899	4 weeks	Corticosteroids	123	NOS: 6/9
Medikonda et al.[922]	435	379 #	54	262/173	R	Brain	0	56	379	3 months	Surgery and corticosteroids	24	NOS: 3/9
Mayer et al.[923]	106	106	NS	NS	R	Brain	NA	12	94	8 to 17 months	Chemotherapy, radiotherapy and surgery	55	NOS: 6/9
Prasad et al.[924]	919	919	≈50	0/919	R	Breast	0	213	706	Estimated ≈ 9 months based on the typical duration of surgery, chemotherapy, radiotherapy, and immediate post-radiotherapy follow-up.	Chemotherapy, radiotherapy, surgery, and corticosteroids	521	NOS: 6/9
Prasad et al.[925]	208	208	≈48	0/208	P	Breast	0	0	208	≈ 9 months	Chemotherapy, target therapy, radiotherapy, and corticosteroids	81	NOS: 6/9
Accordino et al.[926]	14506	14506	≈75	162/ 14344	R	Breast	NA	0	14506	2 years	Chemotherapy, corticosteroids, surgery, and radiotherapy	3234	NOS: 9/9

Cheung et al.[927]	62	62	61	0/62	R	Breast	NA	4	58	3-4 months	Target therapy and hormonal therapy	40	NOS: 3/9
Almodallal et al.[928]	51	51	71	1/50	R	Breast	NA	10	41	2.6 months	Target therapy	37	NOS: 2/9
Ge et al.[929]	92	92	59.9	0/92	R	Breast	9	31	52	117 days	Target therapy and hormonal therapy	59	NOS: 5/9
Lu et al.[930]	128	128	50.8	0/128	P	Breast	NA	0	128	≈ 3 months	Surgery and/or chemotherapy	82	NOS: 6/9
Ji et al.[931]	119	114	50.1	0/119	R	Breast	NA	5	114	18 months	Surgery and chemotherapy	78	NOS: 6/9
Juanjuan et al.[932]	1434	1283 #	20–80	0/1434	R	Breast	NA	151	1283	41 months	Surgery, chemotherapy, radiotherapy, endocrine therapy, and targer therapy	131	NOS: 7/9
Vernieri et al.[933]	801	722	63	0/801	R	Breast	79	0	643	3 months	Hormonal therapy, target therapy and antidiabetic	186	NOS: 9/9
Kjærgaard et al.[934]	74526	74526	≈62	0/74526	R	Breast	NA	0	74526	5 years	Endocrine therapy, chemotherapy, surgery, radiotherapy, surgery, and target therapy	5607	NOS: 9/9
Ma et al.[935]	30	30	55	0/30	NRCT-I	Breast	NA	0	30	≈ 3 months	Target therapy, hormonal therapy, and corticosteroids	6	ROBINS-I : serious
Pancirov et al.[936]	23	23	63	0/23	RCT-II	Breast	11	0	12	3 months	Target therapy and hormonal therapy	22	RoB 2: high risk
Rugo et al.[937]	284	284	62	0/284	RCT-III	Breast	159	12	113	≈6 months	Target therapy and hormonal therapy	181	RoB 2: low risk
	287	287	64	0/287	RCT-III	Breast				≈6 months	Placebo plus hormonal therapy	28	RoB 2: low risk
Margonis et al.[938]	306	306	57	167/139	R	Color	NA	49	257	Day of surgery	Surgery	170	NOS: 7/9
Feng et al.[939]	362	362	≈60	NS	R	Color	0	0	362	40 months	Chemotherapy, and corticosteroids	83	NOS: 6/9
Krag et al.[940]	46373	46373	70	24236/ 22137	R	Color	0	0	46373	4.1 to 4.7 years	Surgery and chemotherapy	2556	NOS: 9/9
Kim et al.[941]	2314	2314	60.5	0/2314	R	Endo	NA	0	2314	5 years	Surgery, radiotherapy, and chemotherapy	682	NOS: 9/9
Nan et al.[942]	202	202	57	0/202	R	H&N	14	0	188	3-4 months	Chemotherapy and corticosteroids	11	NOS: 3/9
Nguyen et al.[943]	106	91 #	59	105/1	R	H&N	NA	16	91	≈several months (≈2–4 months), depending on the number of chemoradiotherapy cycles.	Chemotherapy, corticosteroids, antiemetic, and radiotherapy	11	NOS: 3/9
Mellor et al.[944]	282	253 #	≈57	235/47	R	H&N	NA	29	253	54 months	Chemotherapy, radiotherapy, and corticosteroids	8	NOS: 3/9

Weiser et al.[945]	278	278	39	183/95	R	Leuk	NA	20	258	30 days	Chemotherapy and corticosteroids	103	NOS: 7/9
Dare et al.[946]	144	144	≈6.5	82/62	R	Leuk	NA	0	144	35 days	Chemotherapy, corticosteroids	100	NOS: 3/9
Baillargeon et al.[947]	155	155	<18	98/57	R	Leuk	NA	0	155	28 days	Chemotherapy and corticosteroids	17	NOS: 3/9
Vaswani et al.[948]	76	76	31.93	44/32	R	Leuk	0	9	67	Short follow-up likely limited to hospitalisation duration (probably days to weeks)	Corticosteroids and chemotherapy	64	NOS: 7/9
Tsai et al.[949]	133	133	<18	76/57	R	Leuk	0	0	133	5 weeks	Corticosteroids and chemotherapy	22	NOS: 7/9
Yetgin et al.[950]	26	26	5.01±3.35	17/9	P	Leuk	11	0	15	60 days	Corticosteroids and chemotherapy	6	NOS: 7/9
Zhang et al.[951]	159	159	4.7	117/42	R	Leuk	0	0	159	3.2 years	Chemotherapy and corticosteroids	38	NOS: 5/9
Suo et al.[952]	156	156	34.5	87/69	R	Leuk	NA	0	156	24.7 months	Chemotherapy and corticosteroids	33	NOS: 6/9
Roberson et al.[953]	871	871	NS	485/386	R	Leuk	NA	0	871	4-5 weeks	Corticosteroids and chemotherapy	141	NOS: 7/9
Sonabend et al.[954]	135	135	7	64/71	R	Leuk	NA	0	135	4 weeks	Corticosteroids and chemotherapy	75	NOS: 7/9
Sonabend et al.[955]	167	167	7±4.1	81/86	R	Leuk	NA	0	167	4 weeks	Chemotherapy and corticosteroids	97	NOS: 7/9
Koltin et al.[956]	363	363	<10 (79.3%) and ≥10 (20.7%)	222/141	R	Leuk	NA	0	363	8 to 14 days	Chemotherapy and corticosteroids	57	NOS: 7/9
Aisyi et al.[957]	57	57	6,7	39/18	P	Leuk	0	0	57	4 weeks	Chemotherapy and corticosteroids	3	NOS: 7/9
Pui et al.[958]	421	421	6.8±0.2	249/172	R	Leuk	0	0	421	4 weeks	Chemotherapy and corticosteroids	41	NOS: 6/9
Yu et al.[959]	43	43	32	29/14	R	Leuk	0	0	43	3 to 6 months	Target therapy	11	NOS: 3/9
	102	102	35	66/36	R	Leuk	0	0	102	3 to 6 months	Target therapy	19	
	225	225	38	144/81	R	Leuk	0	0	225	3 to 6 months	Target therapy	28	
Iwamoto et al.[960]	25	25	63	15/10	R	Leuk	0	4	21	2 years	Target therapy	9	NOS: 3/9
Aydin et al.[961]	30	29	59.97	19/11	R	Lung	0	3	27	4 days	Surgery and chemotherapy	12	NOS : 6/9
Sequist et al.[962]	130	130	≈60	30/100	NRCT-I/II	Lung	*	12	118	10.5 weeks	Target therapy	47	ROBINS-I : serious
Lee et al.[963]	83	83	57 (34–86)	39/44	R	Lym	NA	0	83	49 months	Radiotherapy and H. pylori eradication	7	NOS: 3/9

	142	142	55 (31–86)	48/94	R	Lym	NA	0	142	49 months	H. pylori eradication	2	
Baek et al.[964]	17	17	55±7.0	8/9	R	Lym	0	0	17	47 months	Radiotherapy and H. pylori eradication	6	NOS: 4/9
	62	62	53±9.0	32/30	R	Lym	0	0	62	54 months	H. pylori eradication	18	
Lamar et al.[965]	160	160	61.1	95/95	R	Lym	NA	43	117	5 years	Immunotherapy, chemotherapy and corticosteroids	75	NOS: 7/9
Lee et al.[966]	80	80	57	39/41	R	Lym	NA	0	80	4-6 weeks	Immunotherapy, chemotherapy and corticosteroids	26	NOS: 7/9
Agarwal et al.[967]	130	130	NS	NS	R	Mela	0	0	130	61 days	Immunotherapy and corticosteroids	27	NOS: 2/9
Gauci et al.[968]	116	58	62.5	60/56	R	Mela	NA	0	116	7 months	Immunotherapy and corticosteroids	7	NOS: 1/9
Jung et al.[969]	155	155	61	78/77	R	Myel	NA	0	155	60 days	Corticosteroids and chemotherapy	64	NOS: 7/9
Du et al.[893]	100	100	54.30 ± 10.63	0/100	R	Ovary	0	0	100	5 years	Surgery and chemotherapy	32	NOS: 7/9
Alpertunga et al.[970]	73	73	72	38/35	R	Pancr	NA	25	45	1-year	Surgery, corticosteroids, and chemotherapy	28	NOS: 2/9
White et al.[971]	101	59 #	64.3 ± 10.7	57/44	R	Pancr	NA	42	59	6 months	Surgery, chemotherapy, and radiotherapy	12	NOS: 1/9
Bahl et al.[972]	1382	1382	NS	1382/0	R	Pros	NA	333	1049	36 months	Hormonal therapy and corticosteroids	84	NOS: 5/9
Jhan et al.[973]	4604	4604	73.05	4604/0	R	Pros	NA	0	4604	4.04±2.88 years	Hormonal therapy	512	NOS: 9/9
Keating et al.[974]	37443	22356	66.9	37443/0	R	Pros	NA	15087	22356	2.6 years	Hormonal therapy	4967	NOS: 9/9
Ziaran et al.[975]	95	95	73.3 ± 6.2	95/0	P	Pros	NA	0	95	24 months	Hormonal therapy, radiotherapy and surgery	4	NOS: 7/9
Derweesh et al.[976]	396	396	71.7	396/0	R	Pros	NA	77	319	60.1 months	Hormonal therapy and radiotherapy	113	NOS: 6/9
Tsai et al.[977]	12191	12191	NS	12191/0	R	Pros	NA	113	12191	4.8 years	Hormonal therapy	1203	NOS: 9/9
Basaria et al.[978]	18	18	70.2±1.8	18/0	R	Pros	NA	0	18	12 months	Hormonal therapy	8	NOS: 6/9
	17	17	65.9±2.5	17/0	R	Pros	NA	0	17	12 months	Surgery and/or radiotherapy	2	
Yang et al.[979]	32	32	57.3±13.0	16/16	R	Var	NA	7	25	3 to 6 months	Surgery and corticosteroids	18	NOS: 2/9
Sopfe et al.[980]	344	344	8	204/140	R	Var	NcA	0	344	114 days	Surgery, immunosuppressive agents, corticosteroids and radiotherapy	151	NOS: 7/9
Yang et al.[981]	2029	2029	NS	NS	R	Var	NA	0	2029	Short follow-up likely limited to chemotherapy duration (probably weeks to months)	Chemotherapy	331	NOS: 2/9

Lee et al.[982]	270	270	51.0±8.9	64/206	P	Var	NA	0	270	39 months	Chemotherapy and corticosteroids	17	NOS: 8/9
Healy et al.[983]	168	168	57.1±14.4	99/69	R	Var	NA	39	129	4 days	Corticosteroids	65	NOS: 1/9
Schultz et al.[984]	131	131	68	89/42	P	Var	7	0	124	12 days	Corticosteroids, radiotherapy, and surgery	56	NOS: 7/9
Vidler et al.[985]	34	34	58.6 (22–87)	21/13	P	Var	NA	7	27	3-4 months	Corticosteroids and chemotherapy	15	NOS: 5/9
Gonzalez-Gonzalez et al.[986]	32	32	38.4±18.7	15/17	P	Var	0	0	32	6 to 12 weeks	Corticosteroids	22	NOS: 7/9
Leiter et al.[987]	385	385	≈66	239/146	R	Var	NA	86	299	6 months	Immunotherapy, chemotherapy and corticosteroids	102	NOS: 7/9
Mulla et al.[988]	959	959	61.2	NS	R	Var	NA	103	856	12 months	Immunotherapy and corticosteroids	131	NOS: 4/9
Lee et al.[989]	1105	1105	60.2±12.3	676/429	R	Var	NA	0	1105	Mean ≈ 7 months	Chemotherapy	54	NOS : 9/9
	221	221	60.4±12.8	136/85	R	Var	NA	0	221	Mean ≈ 7 months	Immunotherapy	33	
Gómez-Sámano et al.[990]	106	106	40.2±16.7	56/50	R	Var	19	11	76	6 months	Target therapy	0	NOS: 6/9
Geuna et al.[991]	387	387	59.7	194/193	R	Var	NA	0	387	94.6 days	Target therapy	335	NOS: 1/9
	109	109	56.3	56/53	R-CC	Var	NA	0	109	124.7 days	Target Therapy	88	
Yoo et al.[992]	632	618	51	171/461	R	Var	NA	42	590	97 days	Chemotherapy, corticosteroids, radiotherapy, and surgery	85	NOS: 4/9
Harris et al.[889]	90	90	59.6	50/40	P	Var	NA	25	65	14.6 days (Chemotherapy) and 148 days (bone marrow transplantation)	Corticosteroids, chemotherapy, radiotherapy, and surgery	53	NOS: 1/9
Lyall et al.[993]	16	16	60.1	0/16	P	Var	1	0	15	5 days	Corticosteroids and chemotherapy	15	NOS: 6/9
Welsch et al.[994]	267	267	≈9	170/97	R	Var	NA	0	267	3 to 33 months	Chemotherapy, corticosteroids, Radiotherapy, surgery	40	NOS: 7/9
Jeong et al.[995]	77	77	59	55/22	P	Var	NA	0	77	6 months	Chemotherapy and corticosteroids	17	NOS: 8/9
Ose et al.[892]	3512	3512	57.8	1788/1724	P	Var	211	429	2872	28 months	Surgery, chemotherapy, radiotherapy, Hormone therapy, Immunotherapy, corticosteroids	1890	NOS: 6/9
Moore-Vasram et al.[996]	19530	19530	59±17	11026/8504	R	Var	NA	3950	15580	2.4 years	Corticosteroids, chemotherapy, Radiotherapy	3705	NOS: 7/9

Majhail et al.[997]	180	180	27	102/78	R	Var	NA	24	156	2 years	Surgery, corticosteroids, radiotherapy and chemotherapy	54	NOS: 7/9
DiSano et al.[998]	115	115	57.7	NS	R	Var	NA	6	109	24h after surgery	Surgery, corticosteroids, and Insulin	68	NOS: 5/9
Guo et al.[999]	290	290	≈48	157/133	R	Var	NA	23	267	2-day after surgery	Surgery and corticosteroids	10	NOS: 1/9
Busaidy et al.[1000]	57	57	39	28/29	NRCT-I	Var	NA	3	54	21.4 months	Target therapy	36	ROBINS-I : serious

Notes. Quality assessed according to a modified Newcastle Ottawa Scale (range 1-9, with 1-3 indicating low quality, 4-6 indicating moderate quality, and 7-9 indicating high quality). **Legend**. **Db-BF**: Diabetes before TTT (N); **Follow-up**: Median follow-up of blood glucose measurements; **HGl-AFT**: Total any grade hyperglycemic events post-treatment (N); **Local**: localization of cancer; **N**: sample size; **NA**: Not Assessed; **N(aft)**: number of patients with data after treatment; **NMGl-BF**: Normoglycemia before TTT (N); **NRCT-I**: Non Randomized Controlled Trial (phase I); **NRCT-I/II**: Non-random controlled clinical trial (phase I-II); **NS**: Not Specified; **P**: prospective study; **PDb-BF**: Pre-diabetes before TTT (N); **R**: retrospective study; **R-CC**: Retrospective Case-Control; **RCT**: randomized controlled trial; **RCT-II**: Randomized clinical trial (phase II); **RCT-III**: Randomized controlled trial (phase III); **Ref**: reference; **Sd**: standard deviation; **TTT**: Treatment studied; *: including in diabetes; #: only non diabetic. For localizations of cancer: **Color:** colorectal; **Endo**: Endometrial; **H&N**: Head & Neck; **Leuk**: Leukemia; **Lym**: Lymphoma; **Mela**: Melanoma; **Myel**: Myeloma; **Pancr**: Pancreas; **Prost**: Prostate; **Var**: Various.

Considering the 91 studies included in the analysis, of the 222,862 patients for whom data were available, the overall percentage of post-treatment hyperglycemia across all grades was 30,005 individuals (13.44%). For studies focusing exclusively on any grade hyperglycemia (68 studies excluding specific diabetes studies), including 40,491 individuals, the hyperglycemia any grade percentage was 10,539 (26 %). Meanwhile, for studies that focused on patients with diabetes (23 studies), which included 182,371 individuals, there were 19,416 post-treatment diabetics (10.6%). Overall, the most used therapies across these studies were corticosteroids (64%), chemotherapy (57%), surgery (37%), and radiotherapy (29%). The glucose estimators and values used in these studies cover a wide range, all raw data of the systematic review are available in Supplementary Material 2.

Meta-analysis

A meta-analysis of 28 studies including 54,659 patients revealed extremely high heterogeneity (I^2=98.90%), suggesting substantial variability among the included studies. All the studies were selected under the condition that they had precise data on hyperglycemia and/or type 2 diabetes at baseline and after treatment. The Freeman-Tukey random effects model provided a combined effect estimate of θ_{RE}=0.7230 (CI_{95}=[0.6133-0.8326]), indicating a significant effect of treatment induced hyperglycemia. The inter-study variance (τ) was 0.2840, suggesting moderate variance on the effect scale. The difference in proportions between groups was 24.05% (CI_{95}=[14.71-33.40]), indicating a statistically significant difference (see Figure 2 below).

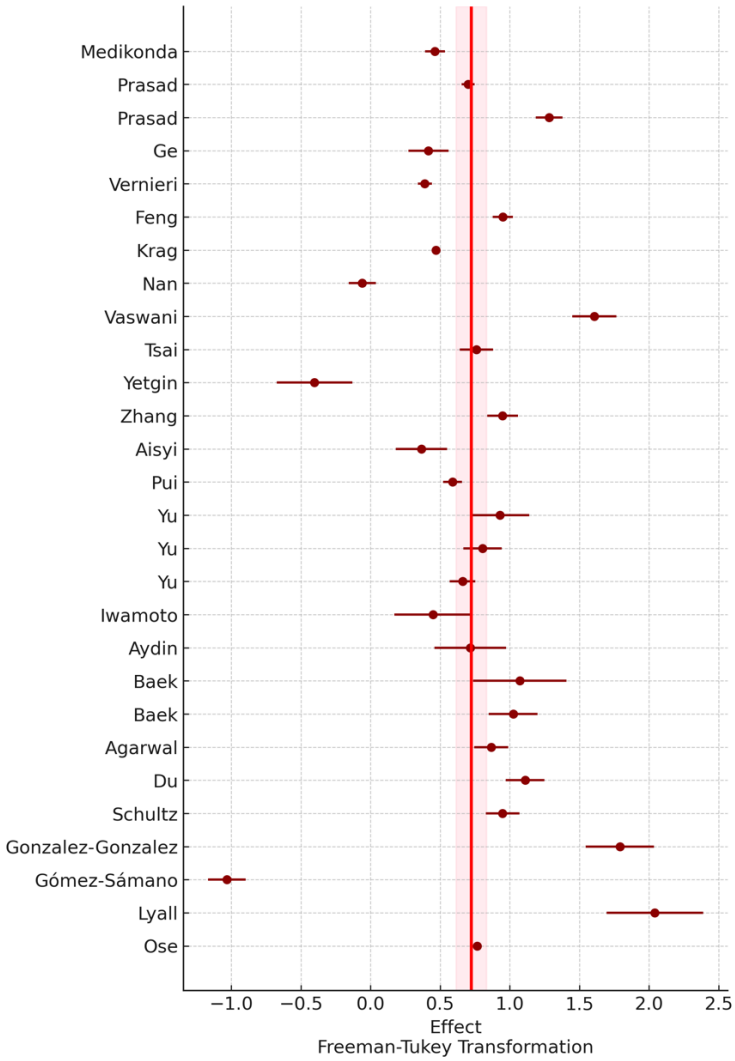

Figure 7.2. Effect of treatment on hyperglycemia across 28 studies using the Freeman–Tukey double–arcsine transformation and a random-effects model (DerSimonian–Laird).
The forest plot displays the individual study effect sizes (Δ Freeman–Tukey–transformed proportions of hyperglycemia before versus after treatment) and their 95% confidence intervals. Effect sizes were calculated as the difference between the Freeman–Tukey double–arcsine–transformed proportions of hyperglycemia after and before treatment in each study. The variance of each transformed difference was approximated as 1/(2n), consistent with standard variance-stabilizing procedures. The pooled effect was estimated using a random-effects model (DerSimonian–Laird method) because heterogeneity across studies was extremely high ($Q=2454.46$ with $p<0.0001$, degrees of freedom$=27$; $I^2=98.90\%$; $\tau=0.2840$). The vertical line represents the pooled random-effects estimate ($\theta_{RE}=0.7229$), and the shaded area represents its 95% Confidence Interval ($CI_{95}=[0.6133-0.8326]$). Higher positive values indicate a larger increase in hyperglycemia prevalence after treatment on the transformed scale.

Subgroups meta-analysis

A subgroup analysis was conducted to examine the effect of treatment based on different variables. We performed 9 distinct analyses for the following factors: type 2 diabetic patients,

non-diabetic patients, patients treated with corticosteroids, patients not treated with corticosteroids, monotherapy, combination therapy, very short-term follow-up (<1 month), short-term follow-up (1 month to 1 year), and mid-term follow-up (1 year to 5 years). In patients treated with corticosteroids, the combined effect on hyperglycemia showed an increase of 28.86% (CI_{95}=[12.85-44.88]), whereas for those without corticosteroids, the increase was 18.25% (CI_{95}=[8.34-28.16]). This highlights the impact of corticosteroids on glucose metabolism, a factor that must be considered when monitoring oncology patients. Patients receiving combination therapies showed a higher prevalence of hyperglycemia, with a combined effect of 27.76% (CI_{95}=[13.67-41.85]), while those undergoing monotherapy had an increase of 19.52% (CI_{95}=[5.81-33.24]). This suggests that combination treatments may have a more pronounced impact on the induction of hyperglycemia, justifying closer glucose monitoring in this group. Short-term follow-up showed a 17.46% (CI_{95}=[4.46-30.46]) increase in hyperglycemia prevalence, while medium-term follow-up showed an increase of 22.83% (CI_{95}=[12.16-33.50]). Another analysis was conducted due to the presence of low-quality studies. By excluding those with a NOS score below 5 (N=9), the estimate obtained using the random effects model (Freeman-Tukey) reveals a significant combined effect of $\theta_{RE} = 0.7447$ (CI_{95}=[0.6097-0.8798]). The inter-study variance (τ) is moderate, at 0.2898. The results remained very similar even after excluding these low-quality studies, with the heterogeneity (I^2=99.18%) also remaining unchanged.

The results of the analyses are summarized in the following Table 3, with an estimation of the combined effect for each subgroup, showing a significantly increased prevalence of hyperglycemia after treatment in each studied subgroup. Heterogeneity remains extremely high (I^2>97%) in all cases, highlighting the substantial variability across the included studies. All details of the subgroup analyses and their results are provided in the Supplementary Material 3.

Table 7.3. Summary of the subgroup meta-analysis

Sub-group	N	I^2 (%)	Tau τ	Combined effect* θ_{RE}[CI_{95}]	Effect % [CI_{95}]
All studies that exclusively evaluate hyperglycemia in the context of type 2 diabetes	11	97.93	0.1509	0.5199 [0.4234-0.6164]	16.15 [6.93-25.36]
All studies except those that strictly and solely evaluate type 2 diabetes	24	98.51	0.3479	0.7702 [0.6268-0.9135]	25.39 [14.79-35.98]
With corticosteroids	15	98.34	0.3091	0.8268 [0.6653-0.9883]	28.86 [12.85-44.88]
Without corticosteroids	13	98.60	0.3316	0.6003 [0.4137-0.7869]	18.25 [8.34-28.16]
Monotherapies	13	98.69	0.5821	0.6412 [0.3207-0.9617]	19.52 [5.81-33.24]
Combination therapies	15	99.10	0.2471	0.7960 [0.6654-0.9266]	27.76 [13.67-41.85]
Very short-term	7	97.41	0.4443	1.0376 [0.7002-1.3750]	38.76 [11.23-66.30]
Short-term	15	99.01	0.3773	0.5510 [0.3568-0.7453]	17.46 [4.46-30.46]
Mid-term	6	98.25	0.3369	0.8154 [0.5348-1.0959]	22.83 [12.16-33.50]

Notes. Freeman-Tukey random effect model. N = number of studies.

In all the meta-analyses conducted, the effect of the treatment on induced hyperglycemia was always statistically significant.

7.4 Discussion

This study reinforces that treatment-induced hyperglycemia is a prevalent side effect of oncological therapy, but it also highlights that this risk manifests at all stages of cancer care, including very short-, short-, and medium-term phases. Indeed, our subgroup analyses revealed significant variations in the prevalence of hyperglycemia based on several factors, underscoring the importance of considering these variables to better understand the effects of treatments on glycemia. The meta-analysis of the 28 included studies (totaling 54,659 patients) revealed extremely high heterogeneity (I^2=98.90%), suggesting substantial variability across the studies. The combined effect estimate revealed a statistically significant difference of 24.05% (CI_{95}=[14.71-33.40]), indicating a marked effect of treatment on hyperglycemia. However, it is important to note that the between-study variance (τ=0.2840) remains moderate, reflecting possible differences in the effect across the studies. Subgroup analysis revealed that treatment led to a significant increase in the prevalence of hyperglycemia in all examined subgroups. These results suggest that the impact of treatments on glycemia may be more pronounced in the mid-term, with residual effects potentially persisting after the completion of treatment**.** As

shown in Table 1, hyperglycemia and diabetes consistently represent unfavorable prognostic factors for survival across nearly all cancer types.

The role of glucose as a fermentable fuel for cancer cells is well-established [885, 886, 1001]. Indeed, for example, the end product of aerobic glycolysis (Warburg effect) is lactate [885,1002], which can induce cachexia [1003,1004]. This represents a physiological association leading to a poor prognosis, as cachexia affects approximately 33% of all cancer patients, with cachectic patients exhibiting a 58% higher risk of death [1005]. In addition, an in vivo study demonstrated that tumor- and chemotherapy-induced cachexia causes significant loss of body weight and skeletal muscle mass, increased glucose utilization, and specific metabolic alterations (TCA cycle, β-oxidation) [1006]. Furthermore, it is well known that several anticancer therapies can induce cachexia [1007–1009]. In light of our study results, it would be prudent to proactively manage the care of cancer patients receiving standard treatments with consideration for the impact of therapies on glucose metabolism. For example, glucose infusions (such as dextrose) are frequently used during surgeries for cancer patients [1010,1011], which could potentially have detrimental effects on patient survival. Importantly, while dextrose infusion can mitigate postoperative nausea and vomiting, it is often elective and non-insulinogenic alternatives are available [1012,1013]. Additionally, postoperative hyperglycemia has been associated with a shorter survival due to an increased risk of death from infections [893, 894]. The use of corticosteroids should also be reconsidered, as they have been associated with shorter survival [887]. Indeed, some studies in brain cancers have shown that lower doses of dexamethasone provide the same therapeutic benefits as higher doses, while being associated with significantly fewer adverse effects [1014,1015]. Among the potential alternatives for cancer management, the ketogenic diets could be a viable option for cancer patients. Indeed, a systematic review and meta-analysis has shown that ketogenic diet reduces blood glucose levels [1016]. Another meta-analysis in mice suggested that ketogenic diets alone can prolong survival and slow tumor progression compared to carbohydrate-rich diets[1017]. The ketogenic diet is characterized by very low carbohydrates, moderate protein, and high fat intake. A study suggests that high pre-treatment carbohydrate intake may be associated with poorer prognosis in head and neck squamous cell carcinoma patients, while moderate fat intake post-treatment could be beneficial [1018]. Nevertheless, not all ketogenic diets are equivalent, which is why a monitoring biomarker, the Glucose–Ketone Index (GKI), has been developed. The optimal therapeutic levels characterized by glycemia below 5 mM and ketonemia above 1–2 mM, maintaining GKI values below 2.0 [1019,1020]. Indeed, there is an inverse correlation between glucose and ketones, thereby reducing a fermentable and essential fuel for cancer cells

in favor of a secondary oxidative fuel, which in turn reduces tumor progression [1021,1022]. Preliminary clinical evidence suggests that tumor progression is markedly reduced in glioblastoma when these measures are strictly followed, resulting in approximately an eight-fold increase in 3-year survival in the adherent group [1023]. Moreover, when a ketogenic diet is combined with cytotoxic drugs, it may reduce the associated drug side effects [1021]. In addition to dietary interventions, regular physical activity is associated with reduced blood glucose levels in breast cancer [1024]. Bacurau et al. [1025] investigated the effect of high-intensity exercise on tumors in rats. Exercise reduced tumor growth by altering tumor cell glucose and glutamine metabolism, while also decreasing lactate production and glutamine decarboxylation. These metabolic changes were accompanied by an attenuation of cachexia symptoms, including excessive weight loss and reduced food intake. It was recently shown in two syngeneic murine tumor models of breast cancer and lung cancer that both acute (swimming) and regular (voluntary running) physical activity reduce systemic glutamine availability (the second fermentable fuel with glucose), thereby limiting tumor growth and protecting against muscle mass loss [1026]. For instance, corticosteroids are also known to increase glutamine levels [1027].

Based on these findings, we suggest particular attention at each stage of patient follow-up:

(i) daily blood glucose monitoring in patients with cancer, whether diabetic or not, during the treatment period;
(ii) monitoring should pay particular attention to blood glucose variations, not just diabetic thresholds during and after cancer treatment;
(iii) glucose infusion (or its derivatives) should be removed from surgeries for cancer patients;
(iv) corticosteroids should be used in oncology only when unavoidable (e.g., emergencies or specific lymphoproliferative cancers), at the minimum effective dose, with regular reassessment and gradual tapering whenever possible;
(v) enhanced and careful glucose monitoring for pre-cachectic or cachectic patients during treatments;
(vi) a ketogenic diet inducing nutritional ketosis, with monitoring of the GKI, may be a relevant strategy to counteract the potential hyperglycemic effects of conventional treatments;
(vii) moderate physical activity should be encouraged whenever possible to reduce blood glucose levels and prevent cachexia.

The main limitations of this study stem from the high heterogeneity of the data, which can be attributed to several factors. First, the absence of frequent and reliable blood glucose measurements in oncology contributes to variability. Additionally, the lack of a consistent paired contingency table led to assumptions of independence between proportions, which might either underestimate or overestimate variance, especially when within-subject correlations are high. The Freeman-Tukey transformation, which is not strictly linear, further complicates the interpretation of differences in proportions. In many studies, hyperglycemia events were not reported prior to treatment, leading to extreme values after transformation. Moreover, the diversity of the included studies (including different cancer types, therapeutic regimens (monotherapy vs. combination therapy), and follow-up periods) contributes to this heterogeneity. This variability was also observed in subgroup analyses. Despite these challenges, our meta-analysis consistently demonstrates a significant effect of increased hyperglycemia prevalence following oncological treatment, supporting the relevance of glucose monitoring in cancer patients. While the variability in the studies cannot be disregarded, it does not diminish the significance of the overall effect, which is consistent with known biological effects of cytotoxic, endocrine and glucocorticoid therapies. It is important to note that while the biological effects on glycemia of some therapies such as corticosteroids are well known, correlation analyses do not establish a causal relationship between treatment, hyperglycemia and outcomes. It is possible that patients with worse survival experience more hyperglycemia due to tumor progression and deteriorating metabolic regulation, while patients with better outcomes and overall metabolic health experience less hyperglycemia, despite receiving equivalent treatment. This meta-analysis stands out by not only highlighting the impact of oncological treatments on hyperglycemia and type 2 diabetes, but also by offering insights into the underlying variability of treatment effects. Unlike previous studies, which have disregarded this variability or focused solely on specific cancer types or treatments, our analysis emphasizes the need for standardized glucose monitoring across different oncology settings. Our study also contributes to the current knowledge by providing practical recommendations for improving glycemic management in cancer patients. These recommendations, based on the findings of our meta-analysis, aim to mitigate the negative impact of hyperglycemia on patient outcomes and provide guidance for clinicians to better manage glucose levels in cancer treatment settings.

7.5 Conclusion

The results of this study reveal a significant effect of oncological treatments on the prevalence of hyperglycemia, with a consistent effect across different treatment types, cancer types, and follow-up durations. Improved glycemic management may have a positive impact on patient survival, while further research is needed to better understand the variations. In the future, it would also be of interest to examine how oncologic treatments influence other metabolic pathways of cancer cells.

This chapter therefore emphasizes the risk of hyperglycemia among cancer patients receiving standard-of-care treatments and provides new perspectives for supportive strategies aimed at improving quality of life and potentially enhancing long-term clinical outcomes, including survival. Breath-hold diving represents a discipline at the crossroads of several concepts explored throughout this thesis, particularly the increase in cardiac vagal tone and the reduction of inflammation, lactate levels, and blood glucose concentrations. Therefore, breath-hold diving may represent a promising non-pharmacological approach for future applications in oncology, as well as in the management of chronic and metabolic diseases more broadly.

8. Chapter 8: Conclusions and future perspectives

This document is a core, though not the only, component of my application file for the validation of acquired experience to obtain the doctoral degree from the University of Toulon (in French "Validation des Acquis de l'Expérience, VAE, diplôme de doctorat"). It presents the "analysis of the work and scientific results of one or more research projects" I have conducted throughout my career as a researcher.

By combining experimental observations, critical reviews, and theoretical frameworks, my research aims to deepen our understanding of the interaction between CVT and the tumor environment, and to identify new therapeutic perspectives as part of a comprehensive and emerging field: onco-rhythmology.

As stated in part 2 Chapter 1, the core objective of this research was to explore and better understand the potential role of CVT as a lever for innovation in the emerging field of onco-rhythmology.

Throughout the various chapters and publications, our understanding of the pathophysiology of cancer and the physiology of the vagus nerve, particularly CVT, has been refined and enhanced. Through this multi-faceted approach, the dissertation successfully fulfilled the main objective of exploring CVT as a novel and promising avenue in the field of onco-rhythmology, while also identifying limitations and suggesting future research directions.

A conceptually important refinement that emerges from the body of work presented in this dissertation concerns the functional distinction between vagal afferent and efferent pathways – a distinction that is frequently overlooked in both clinical and experimental contexts, but which is essential for correctly interpreting autonomic data and designing therapeutic interventions. As detailed in Chapter 6, the vagus nerve is predominantly a sensory nerve, with approximately 80% of its fibers transmitting ascending information from visceral organs to integrative brainstem and hypothalamic centers, particularly the NTS and PVN. In cancer, this afferent predominance has a specific pathophysiological consequence: the tumor microenvironment – through its hypoxic, acidic, inflammatory, and mechanical signals – chronically overactivates vagal afferent fibers, which in turn drives sympathoexcitation and suppresses vagal efferent output via central inhibitory mechanisms. Standard HRV indices, including rMSSD and the HF component, reflect cardiac vagal efferent activity mediated by the nA, they do not capture afferent vagal tone. This means that a low HRV in a cancer patient does not simply reflect a globally hypoactive vagus nerve; it reflects a specific suppression of efferent cardiac output in

a context where afferent fibers may be chronically and excessively stimulated. Therapeutic strategies must therefore be designed to selectively restore efferent vagal drive – through trainable brainstem circuits as described in Chapter 5 – rather than broadly "stimulating the vagus nerve," a formulation that risks confounding these two fundamentally distinct physiological vectors.

8.1 Key strengths and limits

One of the main strengths of this body of work lies in its interdisciplinary integration, bridging clinical practice, experimental physiology, and theoretical modeling. The diversity of research settings, ranging from hospital-based studies (Centre Hospitalier d'Avignon) to field-based measurements and collaborations with academic institutions (IFO-GA, J-AP2S), has enriched the robustness and ecological validity of the findings. The proposed physiological models challenge conventional views and propose testable hypotheses grounded in both classical and modern autonomic theory.

However, the field still suffers from a lack of large-scale, high-powered clinical trials validating these approaches. Moreover, methodological heterogeneity across HRV studies remains a limitation for universal application. Another challenge concerns the integration of these approaches into clinical oncology protocols, where pharmacological and radiotherapeutic treatments remain the dominant modalities. Future work must bridge these paradigms through pragmatic trials and interdisciplinary consensus.

8.2 Conclusion on achievements and future perspectives

This manuscript set out to explore whether CVT could serve as a meaningful therapeutic lever in oncology. The answer that emerges from this body of work is nuanced but affirmative. CVT is not simply a prognostic biomarker, it is a modifiable physiological parameter whose suppression reflects, and may in part mediate, the systemic dysregulation characteristic of cancer. Its restoration, through physiologically grounded and trainable interventions, represents a legitimate and underexplored avenue in cancer care.

The research presented here converges on several actionable conclusions. First, CVT can and must be measured rigorously in clinical oncology, using standardized protocols that control for the confounders identified in Chapter 2. Second, not all touch-based or breath-based interventions modulate vagal tone, specificity matters, and breath-hold diving occupies a unique mechanistic position. Third, the tumor microenvironment suppresses vagal efferent activity

through a combination of afferent overstimulation, pro-inflammatory signaling, RAS activation, and dysbiosis, mechanisms that are mutually reinforcing. Fourth, standard treatments aggravate this dysregulation by elevating blood glucose, directly fueling tumor metabolism. The implication is that restoring CVT and managing glycemia are not independent goals, they are two faces of the same metabolic-autonomic intervention strategy.

Chapter 9: References

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