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Gastro-Cardiology: A Novel Perspective for the Gastrocardiac Syndrome

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The gastrocardiac syndrome was coined originally at the beginning of the 19th century to describe an alleged gastric-cardiopathy with reflux heartburn mimicking cardiac chest pain. Today, a wider perspective of gastrocardiac syndrome has emerged. First, the cardiovascular risk factor chronic systemic inflammation may reflect gastroenterological inflammatory conditions, such as inflammatory bowel disease and gastrointestinal infections, in particular, chronic *Helicobacter pylori* infection. Furthermore, since contemporary treatment of cardiovascular disease commonly includes potent antithrombotic medications, the cardiovascular benefit in terms of a decrease in the incidence of recurrent ischemic events and death needs to be carefully balanced with an increased risk of gastrointestinal bleeding. Several strategies to target chronic gastrointestinal inflammation and to diagnose and treat *Helicobacter pylori* to reduce the risk of cardiovascular events and gastrointestinal bleeding are available but residual controversy remains and large-scale gastro-cardiology trials are needed to determine the optimal treatment approaches. In perspective, the centennial gastrocardiac syndrome is more relevant than ever in a contemporary gastroenterology and cardiology setting. A collaborative subspecialty, namely Gastro-cardiology, would introduce novel unique means to study, diagnose and treat gastrocardiac conditions with the aim to reduce the risk of cardiovascular and bleeding events to improve the prognosis for gastro-cardiology patients.

Keywords: gastrocardiac syndrome, *Helicobacter pylori*, cardiovascular disease, upper gastrointestinal (GI) bleeding, atherosclerosis, mortality, myocardial infarction, stroke

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INTRODUCTION

The gastrocardiac syndrome was coined by Ludwig von Roemheld in 1913 to describe an alleged gastric-cardiopathy (1). Contemporary cardiology did however not adopt this diagnosis and reduced the gastrocardiac syndrome to define reflux heartburn mimicking cardiac chest pain. Today, modern cardiology is rapidly developing a close relation to other medical specialties. Cardio-oncology has been formalized, and for example, cardio-rheumatology and cardio-nephrology emerge as subspecialties. The frequent intersections of the roads of gastroenterologists and cardiologists in the centennium following the coining of Roemheld of gastrocardiac provide the perspective to debouch in gastro-cardiology today.

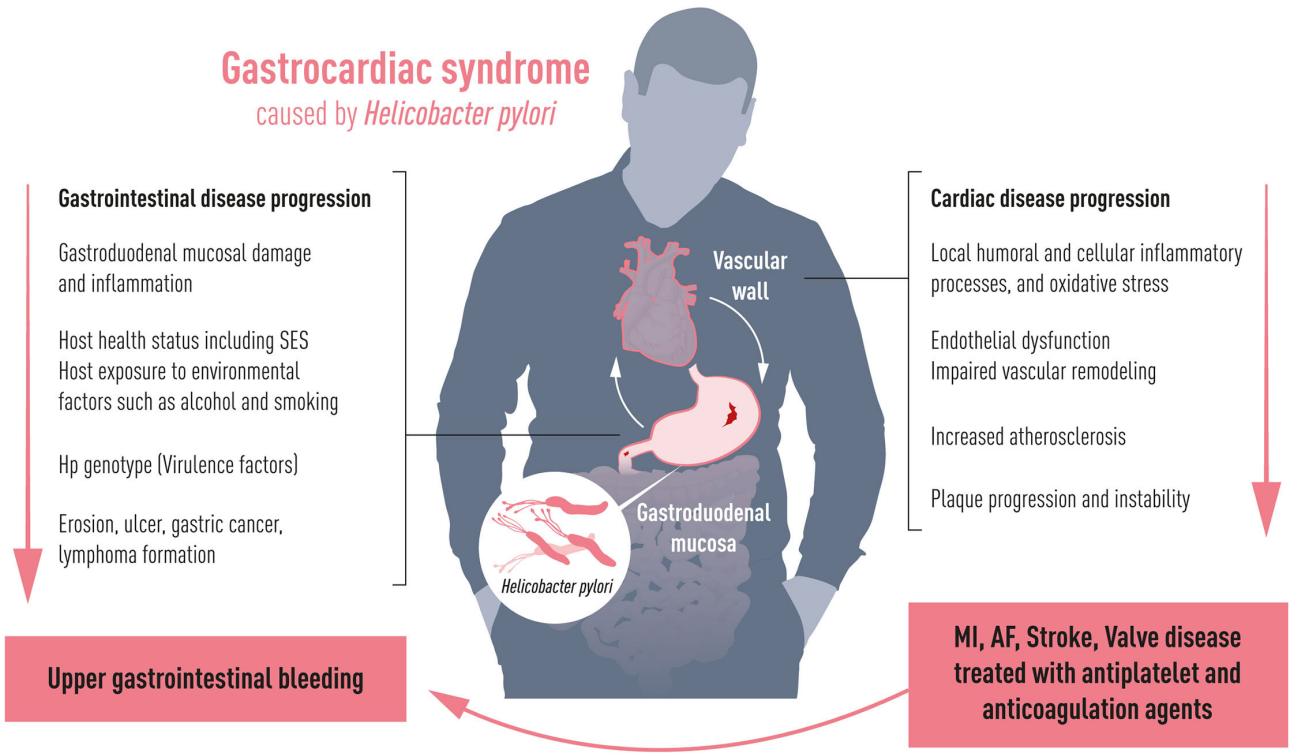

FIGURE 1 | Gastrocardiac syndrome. Depending on host health including socioeconomic status (SES) and virulence factors, *Helicobacter pylori* affects the gastric mucosa causing gastroduodenal lesions with the risk to develop bleeding complications. Simultaneously, it induces chronic inflammation to the vascular wall affecting progress and degree of cardiovascular disease such as stroke, myocardial infarction (MI), atrial fibrillation (AF) and valvular heart disease. Cardiovascular diseases are commonly treated with antithrombotic drugs, which aggravate the risk of upper gastrointestinal bleeding.

CHRONIC SYSTEMIC INFLAMMATION AND CARDIOVASCULAR DISEASE

Chronic systemic inflammation is a well-established cardiovascular risk factor with an underlying immune activation as a major pathophysiological driver in atherosclerosis (2). Chronic inflammation of intestinal origin from Crohn's disease and ulcerative colitis is associated with an increased risk of coronary, cerebrovascular, and peripheral artery disease (3). Trials of anti-inflammatory treatments for optimized cardiovascular prevention and controlled inflammatory bowel disease however differ substantially in terms of the putative therapeutic immune targets (4, 5). Common trial planning, follow-up, analysis, and performance are required to align the research for the optimal gastro-intestinal anti-inflammatory targets. In addition to inflammatory bowel disease, the centenarian gastrocardiac syndrome can today be extended to chronic inflammation through *Helicobacter pylori* (*H. pylori*) infection as an additional ventriculo-duodenal causal factor for atherosclerosis progression and cardiovascular events (6). An almost doubled atherothrombotic cardiovascular risk by *H. pylori* has been established over the last two decades (7). The possible mechanism linking *H. pylori* and atherosclerosis could relate to two pathways: (1) chronic inflammation caused by direct colonization of the vascular wall enhancing and disrupting atherosclerotic lesions, and (2) a systemic inflammatory response in reaction to the colonization of the gastric mucosa (6). Where the first mechanism drives the inflammatory cascade by local and humoral processes toward plaque progression and instability, the latter is influenced by the host health status (e.g., comorbidities such as diabetes) including socioeconomic factors, and host exposure to environmental factors such as smoking and alcohol, all recognized independent predictors of poor cardiovascular outcomes (**Figure 1**). A common gastro-cardiology fight to dampen inflammation can be further encouraged by *H. pylori* being one of the most common chronic infections in the world with an estimated global prevalence of 50% (ranging from 10% in Northern Europe to 80% in Africa) (8) and the potential that lowering inflammation reduces the burden of the most common mortality cause from cardiovascular disease.

GASTROINTESTINAL BLEEDING AND CARDIOVASCULAR DISEASE

Gastrointestinal bleedings have been a common problem in cardiology starting from the discovery of Heyde's syndrome in the past century. Advances since then have deciphered the mechanisms being that blood passage through a stenotic aortic valve increases shear stress to deplete von Willebrand factor. The acquired von Willebrand factor deficiency represents a reverse

causality with the heart causing bleedings from gastrointestinal angiodysplasias in patients with calcific aortic valve stenosis (9). During the last decades, the prognosis for patients with cardiovascular disease, including ischemic heart disease, valvular heart disease, atrial fibrillation, or stroke has remarkably improved. However, the implementation of evidence-based therapies, in particular, the use of antithrombotic treatment presents gastro-cardiological consequences (10). Indeed, the cardiovascular benefit in terms of a decrease in the incidence of recurrent ischemic events and death is counterbalanced by an increase in hemorrhagic complications (11), in particular, from the gastrointestinal tract (12, 13). These typically present as upper gastrointestinal bleedings (UGIB), ranging from a 2-fold increase with low dose aspirin, up to 7-fold with dual antiplatelet treatment, and by a factor of 10 if anticoagulants are co-administered (10). The UGIB complications are not only the direct source for increased morbidity, mortality (14), and medical care costs but may also lead to increased risk of recurrent cardiovascular events due to discontinuation of antithrombotic drugs. Chronic active infection with *H. pylori* may be a common gastric orchestrator of chronic inflammation (6) and UGIB complications in cardiology (10).

Numerous studies over the last two decades have investigated a possible link between *H. pylori* infection and atherothrombotic cardiovascular syndromes and found an association with a two-fold increased risk (7, 15).

While previous studies of *H. pylori* eradication in cardiology aimed to reduce cardiovascular events, the effects of *H. pylori* eradication on reducing cardiological bleeding complications have been somewhat overlooked (16). Several strategies to reduce the risk of UGIB are available. First, the cardiology perspective is a personalized antithrombotic therapy through shortened duration (17) and/or de-escalation (18) based on clinical features and/or risk scores (19–22). Second, the gastroenterologist perspective complies chronic inhibition of gastric acid secretion by proton pump inhibitors (PPI), which are currently recommended in high-risk individuals (defined as a history of gastric ulcer/bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drugs/corticoid steroid use, or two or more of age $\geq$65 years, dyspepsia, gastro-esophageal reflux disease, *H. pylori* infection or chronic alcohol use) (23) to decrease bleeding risk during DAPT post-AMI (24). However, the net benefit of long-term PPI treatment is unresolved. Adverse events include higher rates of chest infections, dementia, cardiovascular events, and chronic kidney disease (24). Further, *H. pylori* eradication which may achieve similar benefits in infected patients while avoiding the side effects and medication costs associated with long-term PPI use (25), is recommended in guidelines, notably, by expert opinion (8, 26). Concerning the mode of *H. pylori* detection, both invasive (gastroscopy-based) and non-invasive (serology, urea breath test [UBT], feces antigen) methods are established (8). As invasive tests imply obvious drawbacks in patients with CV disease with concomitant antithrombotic therapy, the majority of previous studies were based on serological testing to detect *H. pylori*. However, serology does not allow distinction between active and prior *H. pylori* infection, which encompasses diagnostic difficulties, especially from a clinical perspective regarding eradication therapy. Non-invasive screening for active *H. pylori* can be performed with high accuracy (sensitivity 96% and specificity 93%) by UBT (27), currently the recommended diagnostic tool (8). No contemporary data using this mode of detection were available until recently when it was shown in a Swedish multicenter prospective cohort study of 310 consecutive AMI patients that active *H. pylori* diagnosed by UBT were prevalent in 20% of the patients (16), in agreement with previous findings twice as common as in the overall Swedish population with an *H. pylori* prevalence estimated at 11% (28). Importantly, *H. pylori* screening and treatment were feasible in the clinical routine during MI hospitalization. Currently, it is still under debate whether eradication therapy alone is sufficient to prevent recurrent UGIB or if long-term PPI treatment nonetheless remains necessary (29). Thus, gastro-cardiology is needed to address the net benefit of long-term treatments, adverse events, and medication costs of antithrombotic and antiacid treatments, and, critically, to determine how to handle *H. pylori* diagnosis and eradication.

CURRENT FRONTIER OF CLINICAL GASTRO-CARDIOLOGY RESEARCH

To date, the residual controversy on how to handle the risk of UGIB in patients with cardiovascular disease urges the need for randomized gastro-cardiology trials. Recently, the Helicobacter eradication aspirin trial (HEAT), a double-blind, placebo-controlled, randomized trial of the effects of *H. pylori* eradication on subsequent ulcer bleeding in infected individuals taking aspirin daily was completed enrolling 30,000 patients (30). The HELicobacter Pylori screening to prevent gastrointestinal bleeding in patients with acute myocardial infarction trial based on the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (HELP-SWEDEHEART, ClinicalTrials.gov Identifier: NCT05024864) is a cluster-randomized, registry-based clinical trial using SWEDEHEART (31) and other national registries as a trial platform for patient enrollment and data collection. The primary objective is to determine whether systematic screening for *H. pylori* in patients after AMI and subsequent eradication therapy significantly reduces the risk of rehospitalization for UGIB whereas secondary objectives evaluate the incidence of cardiovascular endpoints (rehospitalization for AMI, heart failure, atrial fibrillation, and stroke; cardiovascular and all-cause mortality). Patient enrollment is expected to start in November 2021.

CONCLUSION

In perspective, the centennial gastrocardiac syndrome is more relevant than ever in a contemporary gastroenterology and cardiology setting. A collaborative subspecialty to improve diagnosis and treatment of gastrocardiac conditions and to reduce the cardiovascular risk and complications of ischemic-, arrhythmic- and valvular heart diseases would introduce

novel unique means to improve the outcomes of gastro-cardiology patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

RH and MB: concept and design, critical revision of the manuscript for important intellectual content, and drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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