

Doppler Ultrasonographic Evaluation of Gastrointestinal Hemodynamics in Food Hypersensitivities: A Canine Model

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Chronic enteropathy due to food hypersensitivity is a common complaint in dogs and humans, and definitive diagnosis and identification of offending allergens remains challenging. Doppler waveform analysis of the celiac artery (CA) and the cranial mesenteric artery (CMA) of 8 dogs with proven food hypersensitivity was performed in the fasting state and at 20, 40, 60, and 90 minutes after feeding their regular daily diet, and at 2 and 4 days after feeding 4 different allergens. Resistive index (RI), pulsatility index (PI), and the percentage differences between these measurements were calculated and compared statistically. The maximal decrease in RI and PI after feeding the regular diet was reached at 40 minutes after ingestion in both vessels (CA: RI = -6%, PI = -23%; CMA: RI = -9%, PI = -30%). After this trough, the resistance in both vessels rose nearly to baseline after 90 minutes (CA: RI = -1%, PI = -13%; CMA: RI = -3%, PI = -14%). When fed an allergen-containing meal the percentage changes at the trough were significantly greater (CA: RI = -10%, PI = -32%; CMA: RI = -14%, PI = -40%; $p < 0.05$) compared to those seen after feeding the maintenance diet. Also, RI and PI values were significantly ($P < .05$) lower at 90 minutes on days 2 and 4 of the challenge period. During the challenge period, dogs did not show overt signs of gastrointestinal disease. Significant postprandial hemodynamic alterations in response to food allergens in dogs with food hypersensitivities can be shown noninvasively with Doppler ultrasound.

Key words: Celiac artery; Cranial mesenteric artery; Dietary challenge; Splanchnic blood flow.

Inflammatory bowel disease (IBD) is common in dogs and humans.^{1–5} IBD is a collective term describing a group of chronic enteropathies having histologic evidence of inflammation. In dogs, the nomenclature of the grouping reflects the type of mucosal infiltrate found histologically.² The etiology of IBD in humans is unclear despite extensive investigations in patients with Crohn's disease, celiac disease, and ulcerative colitis.^{1,6} Similarly, the cause of IBD in dogs often is unknown.^{4,6}

One potential cause of IBD is food hypersensitivity leading to chronic alteration of the bowel wall. Food hypersensitivity in dogs and humans is defined as an adverse immunological response to certain food components.^{3,7,8} If a patient is sensitized by a dietary antigen, an immunoglobulin E-mediated allergic reaction may occur and eventually enhance the antigen's transfer through enterocytes, which increases the rapidity of the response. The naturally occurring state of controlled inflammation then is disturbed and local mucosal inflammation due to a cellular and vascular response to those antigens occurs.⁵ Many dietary antigens are known. One of the major contributors of food hypersensitivity is gluten. For example, wheat is an almost ubiquitous food component that contains gluten. Therefore, gluten can act as a prototype in research on food hypersensitivities. Hypersensitivity to gluten has been described in the

Irish Setter and Soft Coated Wheaten Terrier (SCWT).^{9,10} Recent findings on food hypersensitivity in SCWTs have shown them to have a familial syndrome of protein-losing enteropathy that is associated with IBD of varying morphology that may include lymphangiectasia.^{11–13} Their disease has been shown to be multifactorial, including hypersensitivity to various allergens. In humans, gluten is one of the agents contributing to the pathogenesis of celiac disease and its treatment consists of a life-long gluten-free diet.¹⁴ Even trace amounts of gluten in gluten-free-labeled products still can lead to clinically relevant symptoms.¹⁴

Doppler ultrasound provides a noninvasive method of assessing gastrointestinal hemodynamics in dogs and humans.^{15–17} In the early 1930s, the dog was used as a research model for invasive assessment of gastrointestinal circulatory physiology.^{18,19} It was not until the 1980s that Doppler ultrasound was applied to the investigation of human gastrointestinal physiology.^{15,20,21} Similar studies in dogs were not performed until recently. The postprandial hemodynamic response to feeding quantified with transabdominal Doppler ultrasound in healthy dogs is identical to that shown with invasive methods.²²

In chronic enteropathies thought to be due to food hypersensitivity, difficulty often lies in the recognition of the causative allergen.³ The cornerstone of the diagnosis is the restriction diet followed by remission and then relapse of disease when the patient is challenged with the suspected antigen.^{5,8,23} A noninvasive tool to rapidly detect a positive response to a dietary allergen at the mucosal surface in combination with elimination diets and monitoring of dietary therapy would be of potential clinical value. Although Doppler ultrasound has been used to evaluate gastrointestinal hemodynamic physiology and as a diagnostic tool in some enteropathies of humans, to our knowledge Doppler ultrasound has not been used for detecting a response to food allergens.

The purpose of this study is to assess whether spectral waveform analysis of the celiac artery (CA) and cranial mesenteric artery (CMA) can be used to detect hemodynamic alterations when a food allergen is present. We hy-

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Table 1. Results of the previous oral provocation trial of the challenged dogs.

Dog Number	Breed	Allergen							Test Diet
		Corn	Wheat	Soybean	Egg	Milk	Chicken	Lamb	
1	Mix	—	—	—	—	+	—	—	Milk
2	SCWT	?	—	?	—	+	?	—	Milk
3	SCWT	—	—	?	?	—	?	+	Chicken
4	SCWT	—	—	—	—	+	?	?	Milk
5	Mix	—	+	—	—	+	—	—	Milk
6	Mix	—	—	—	—	?	—	—	Milk
7	Mix	—	—	?	—	—	—	—	Soybean
8 ^a	SCWT	+							Corn

SCWT, Soft Coated Wheaten Terrier; —, no reaction; ?, questionable reaction; +, positive reaction, during challenge.

^a Only challenged once because of anaphylactic reaction.

pothesized that dogs with proven food hypersensitivities would have a rapid response to oral allergen in the form of lowered resistance to diastolic flow compared to their response when fed their regular diet. Doppler ultrasound of gastrointestinal vessels may present a new noninvasive diagnostic tool for the diagnosis of food hypersensitivities and a means by which to monitor dietary therapy. Such a diagnostic method may have future applications for investigating the pathophysiology of food hypersensitivities and for monitoring pharmaceutical and dietary therapy in dogs and humans.

Materials and Methods

Study Population

A colony of food-hypersensitive SCWTs and SCWT × Beagle crosses previously established at the North Carolina State University College of Veterinary Medicine was investigated in this study.^{11–13} The study population included 4 SCWTs (age, 5.5 years; weight, 10.8 ± 1 kg; 4 females) and 4 SCWT × Beagle crosses (age, 6 years; weight, 13 ± 2 kg; 1 male and 3 females). The dogs were housed according to animal welfare regulations. This colony was fed a diet formulated for growth until 1 year of age and then changed to a diet formulated for maintenance^a referred to as their regular diet. All dogs were tested for hypersensitivities before this study by an oral provocation dietary trial with several antigens (corn, wheat, soybean, egg, milk, chicken, and lamb).¹² Results of this previous trial are presented in Table 1. For the challenge trial, each dog was given the component it reacted most strongly to except for dog 3, because lamb was not available during the time of the investigations. Therefore, dog 3 was challenged with the component to which it reacted 2nd most strongly (Table 1).

Study Design

Each of the 8 dogs was examined once while fed its regular diet. The dogs then were evaluated a 2nd and 3rd time after being fed an allergen-containing meal.

Doppler ultrasound investigations initially were performed pre- and postprandially when the dogs were fed their regular diet and were free of clinical signs of gastrointestinal disease. The resulting Doppler findings served as the dogs' own control values for later comparison with the allergen-containing test meal. The dogs then were fed a challenge diet for 4 consecutive days and the Doppler examination was repeated on days 2 and 4 of the challenge period. The consistency of the dogs' feces before and during the challenge period was observed and recorded.

Test Meals

The maintenance test meal consisted of a commercial dry dog food^a that was softened with water before feeding. A meal size of 150 cc was chosen to standardize the ingested volume and avoid false results due to the effect of dilatation of the stomach on gastrointestinal blood flow.²⁴ The allergen-containing meal contained either commercially available pure low-fat milk, pure soybean (tofu), pure lean chicken meat, or pure cut corn (according to Table 1). The test meal size in this stage of the study also was 150 cc. Because we have shown that high-fat meals produce exaggerated postprandial hemodynamic responses in healthy dogs, the fat content of the test meals was assessed to insure that the meals were not rich in fat.²⁵ All diets contained <4% of fat according to the manufacturer's nutrition facts.

Ultrasound Examination

Dogs were fasted overnight (at least 12 hours) and examined the next morning at their regular feeding time. They were not exercised before examination to avoid exercise-induced alterations.²⁶ They did not receive any sedatives nor were they anesthetized. Dogs were placed in right lateral recumbency, the hair over the area of the left kidney was clipped, the skin was cleaned with alcohol, coupling gel was applied, and the CA and CMA were imaged from the left lateral abdomen.^{22,25} Measurements in both vessels were made at fasting (t_0) and at 20, 40, 60, and 90 minutes after ingestion of the test meal. During measurements in the fasted state (t_0), the dogs did not have any olfactory or visual contact with the test meals to avoid anticipation-induced effects.

The 2 vessels were identified by using 2-dimensional gray-scale and color Doppler ultrasound as previously described.^{22,25} Each examination was carried out in an identical manner by the same sonographer. A standard image and a vessel-transducer angle < 60° were maintained.^{27–29} The examinations were performed with a Siemens Sonoline Elegra^b ultrasound unit with a 7.5-MHz phased-array transducer. Pulsed spectral Doppler was used to trace the flow in each vessel with a sampling gate size of 2 mm.³⁰ Measurements were made approximately 2 cm from the vessel origin to avoid potential influences by turbulence and vortex shedding produced at sharp turns, such as the origin of the CMA and CA from the aorta.³¹

The peak systolic velocity (PSV), the end-diastolic velocity (EDV), and the mean velocity (MV) of 5 waveforms from each vessel at each time point were calculated by the ultrasound computer via automated tracing. The resistive index (RI = (PSV – EDV)/PSV) and the pulsatility index (PI = (PSV – EDV)/MV) were calculated and the mean of 5 waveforms was used for further analysis.³⁰ The percentage deviation from t_0 for RI and PI was calculated for each time point and for each diet.^{22,25}

Table 2. Blood-flow parameters with mean values and standard deviations of the celiac artery (CA) and the cranial mesenteric artery (CMA) for the regular diet and values of the challenges at day 2 and day 4 in comparison to the values of healthy dogs with a regular maintenance (Kircher) diet.²⁵

	Fasted (t_0)	%	20 minutes	%	40 minutes	%	60 minutes	%	90 minutes	%
CMARI										
Kircher ²⁵	0.819 $\pm$ 0.028	0	0.775 $\pm$ 0.034	-5	0.728 $\pm$ 0.032	-11	0.714 $\pm$ 0.039	-13	0.735 $\pm$ 0.047	-10
Regular diet	0.863 $\pm$ 0.019	0	0.821 $\pm$ 0.019	-5	0.784 $\pm$ 0.031	-9	0.792 $\pm$ 0.028	-8	0.836 $\pm$ 0.022	-3
Day 2 challenge	0.898 $\pm$ 0.018	0	0.806 $\pm$ 0.018	-11	0.775 $\pm$ 0.023	-14	0.787 $\pm$ 0.017	-12	0.79 $\pm$ 0.026	-11
Day 4 challenge	0.904 $\pm$ 0.014	0	0.825 $\pm$ 0.028	-9	0.801 $\pm$ 0.026	-11	0.802 $\pm$ 0.023	-11	0.801 $\pm$ 0.026	-11
CARI										
Kircher ²⁵	0.779 $\pm$ 0.029	0	0.703 $\pm$ 0.049	-10	0.681 $\pm$ 0.025	-13	0.681 $\pm$ 0.044	-13	0.726 $\pm$ 0.037	-7
Regular diet	0.821 $\pm$ 0.031	0	0.776 $\pm$ 0.044	-5	0.773 $\pm$ 0.028	-6	0.793 $\pm$ 0.030	-3	0.814 $\pm$ 0.032	-1
Day 2 challenge	0.872 $\pm$ 0.025	0	0.805 $\pm$ 0.021	-7	0.781 $\pm$ 0.020	-10	0.777 $\pm$ 0.023	-11	0.787 $\pm$ 0.017	-10
Day 4 challenge	0.885 $\pm$ 0.013	0	0.806 $\pm$ 0.032	-9	0.801 $\pm$ 0.019	-10	0.791 $\pm$ 0.021	-11	0.798 $\pm$ 0.015	-10
CMA PI										
Kircher ²⁵	2.418 $\pm$ 0.417	0	1.953 $\pm$ 0.306	-18	1.762 $\pm$ 0.334	-27	1.683 $\pm$ 0.332	-29	1.792 $\pm$ 0.409	-24
Regular diet	3.132 $\pm$ 0.510	0	2.602 $\pm$ 0.406	-17	2.117 $\pm$ 0.221	-30	2.180 $\pm$ 0.260	-31	2.693 $\pm$ 0.228	-14
Day 2 challenge	3.409 $\pm$ 0.364	0	2.234 $\pm$ 0.182	-34	2.034 $\pm$ 0.199	-40	2.150 $\pm$ 0.232	-35	2.249 $\pm$ 0.297	-32
Day 4 challenge	3.598 $\pm$ 0.466	0	2.495 $\pm$ 0.341	-29	2.256 $\pm$ 0.262	-37	2.254 $\pm$ 0.268	-37	2.280 $\pm$ 0.216	-36
CA PI										
Kircher ²⁵	2.076 $\pm$ 0.296	0	1.579 $\pm$ 0.196	-22	1.464 $\pm$ 0.294	-26	1.456 $\pm$ 0.213	-29	1.787 $\pm$ 0.157	-13
Regular diet	2.742 $\pm$ 0.357	0	2.225 $\pm$ 0.373	-19	2.124 $\pm$ 0.211	-23	2.239 $\pm$ 0.230	-18	2.373 $\pm$ 0.255	-13
Day 2 challenge	3.097 $\pm$ 0.487	0	2.292 $\pm$ 0.359	-25	2.049 $\pm$ 0.196	-32	1.931 $\pm$ 0.192	-36	2.148 $\pm$ 0.177	-28
Day 4 challenge	3.366 $\pm$ 0.22	0	2.404 $\pm$ 0.475	-29	2.287 $\pm$ 0.339	-32	2.217 $\pm$ 0.248	-34	2.205 $\pm$ 0.157	-34

Statistical Analysis

Differences between RI and PI values for each dog with respect to time after feeding were assessed by using a linear model. The results were analyzed statistically with a 1-way analysis of variance and the Bonferroni (all-pairwise) multiple comparison test. The computer software NCSS 2001^c was used to compare for differences in RI and PI for each time point as well as between diets.

Results

Mean RI and PI values for the CA and CMA for each meal at each time point as well as the percentage differences from the fasting state (t_0) for all dogs are shown in Table 2. Table 2 also shows the results from a previous study in which healthy dogs were tested with a regular maintenance diet in order to compare them with the measurements obtained in this study.²⁵

Maintenance Diet

Taking the mean of the measurements of all dogs on their regular diet at t_0 , the CMA was characterized by moderate to high resistance flow (mean RI = 0.863 $\pm$ 0.019; mean PI = 3.133 $\pm$ 0.510). The CA had a similar Doppler spectrum (mean RI = 0.821 $\pm$ 0.030; mean PI = 2.742 $\pm$ 0.357) but showed significantly lower values than those of the CMA ($P < .05$). The maximum percent decrease from t_0 in RI and PI after feeding the regular diet was reached at 40 minutes after ingestion in each vessel (CA: RI = -6%, PI = -23%; CMA: RI = -9%, PI = -30%; Fig 1a-d). After this trough, RI and PI in each vessel rose to nearly baseline values at 90 minutes (CA: RI = -1%, PI = -13%; CMA: RI = -3%, PI = -14%). Additionally, values in the CA rose more quickly than those in the CMA.

Challenge Diets

The fasted measurement, t_0 , performed on day 2 of the challenge period was significantly ($P < .05$) greater in the CMA (mean RI = 0.898 $\pm$ 0.018; mean PI = 3.409 $\pm$ 0.364) and CA (mean RI = 0.872 $\pm$ 0.025; mean PI = 3.097 $\pm$ 0.487) compared to t_0 on the regular diet in all dogs. An even larger increase in the CA (mean RI = 0.904 $\pm$ 0.014; mean PI = 3.598 $\pm$ 0.466) and the CMA (mean RI = 0.885 $\pm$ 0.013; mean PI = 3.366 $\pm$ 0.220) was observed on day 4. An example of changes of the waveforms on day 4 is shown in Figure 2.

Compared with the regular diet, challenge diets had percentage changes at the trough significantly ($P < .05$) greater compared to those seen after feeding the regular diet in all dogs (Table 2). After the trough, the RI and PI values tended to stay low even at 90 minutes, which was even more pronounced on day 4 of the challenge period. At 90 minutes, RI and PI values were significantly ($P < .05$) lower on day 2, and on day 4 they decreased even more.

Only 1 of the dogs had intermittent soft feces on day 2 of the challenge. No other dog had abnormal feces or other clinical signs during the challenge period.

Discussion

In humans, Doppler ultrasound has been applied to the assessment of gastrointestinal hemodynamics and diagnosis of pathology in several diseases such as Crohn's disease, celiac disease, and others.³²⁻³⁶ In celiac disease, a hyperdynamic mesenteric circulation has been shown during active disease and normalization has been identified after treatment as detected by Doppler ultrasound of the superior mesenteric and celiac arteries.^{32,37} In this study, we also

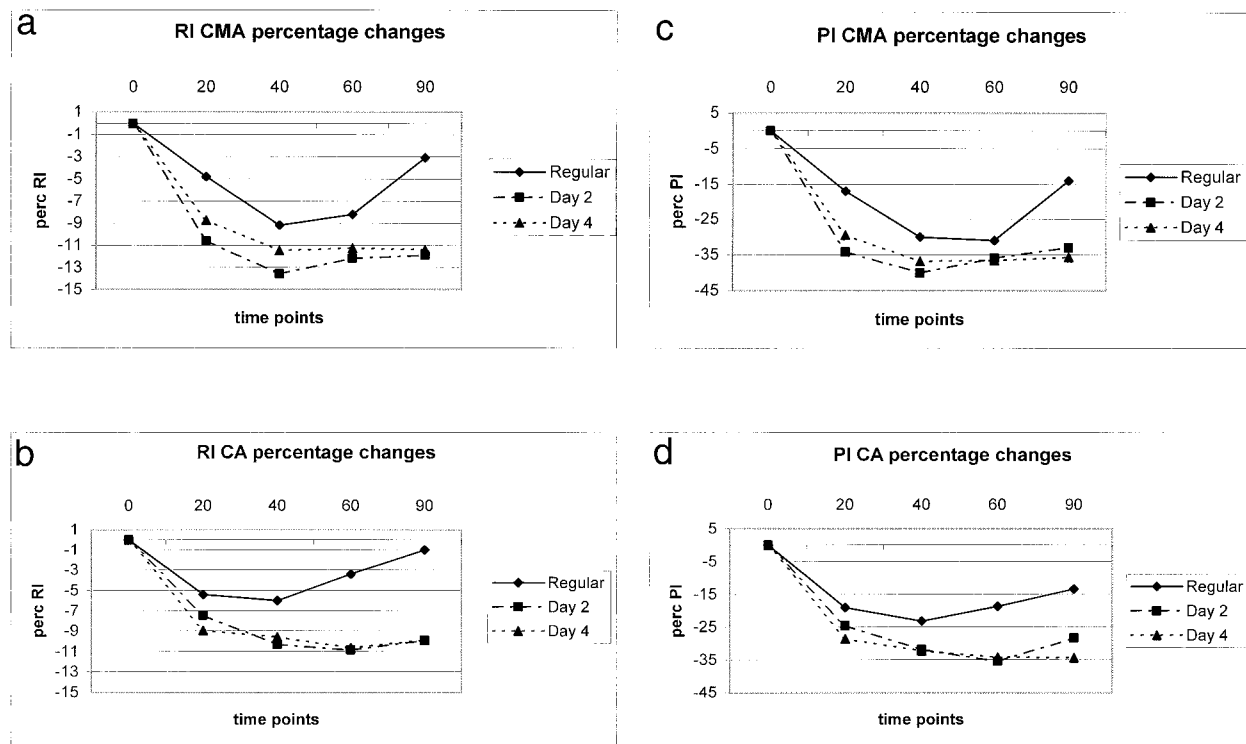


Fig 1. Changes in percentage of (a) resistive index (RI) versus time in the cranial mesenteric artery (CMA), (b) RI in the celiac artery (CA), (c) pulsatility index (PI) in the CMA, and (d) PI in the CA.

have been able to quantify a hemodynamic response in the gastrointestinal tract to allergens in a food-hypersensitive dog model by examining the same arteries with Doppler ultrasound. Significant intraindividual differences were shown between Doppler parameters obtained from a maintenance diet versus an allergen-containing one.

The regular maintenance meal used in this study was not a hypoallergenic one (ie, it contained low concentrations of allergens to which the dogs were known to be sensitive). However, the percentage changes of RI and PI measured with this diet are similar to those from a previous study in healthy dogs.²⁵ The normal hemodynamic response of the gastrointestinal tract of these food-hypersensitive dogs shown with Doppler ultrasound may indicate that their vascular beds have adapted over time to the presence of these small amounts of allergens. The fact that clinical signs of gastrointestinal disease were lacking further supports this hypothesis. The local immune system can become accustomed to chronic stimuli and lower its activity.³⁸ Compared to the effects of a maintenance diet in healthy dogs, the hemodynamic response of the gastrointestinal tract to the regular diet in this study was faster.^{22,25} This finding might be explained by the consistency of the diets used (ie, canned in our previous study versus softened dry food in the present study). The dry version contained less fat, which may have resulted in an earlier 40-minute trough value versus a 60-minute trough value in healthy dogs fed the canned version in a previous study.^{22,25} However, an underlying pathophysiologic cause cannot be ruled out, and should be studied further.

By feeding the dogs a challenge diet that was known to provoke acute disease, we were able to show a significant

decrease in Doppler indices of vascular resistance in both arteries that persisted at 90 minutes. The effects shown on day 2 were similar to the reaction of healthy animals to high-fat diets.^{25,39} The challenge diets were low in fat, more or less resembling high-protein or high-carbohydrate diets to which the gastrointestinal tract responds normally in healthy dogs.^{25,39} Therefore, the reaction in this study most likely is a hemodynamic response to the allergens themselves. A local acute inflammatory response with increased and prolonged vasodilatation would explain the lowered RI and PI values on days 2 and 4 postprandially during the challenge period compared to the regular diet. The release of local vasodilatory mediators such as histamines, interleukins, and others has been demonstrated in different hypersensitivities, such as atopy.⁴⁰ Although these dogs were accustomed to low concentrations of antigens in their diet, when the stimulus was increased over several days, a hemodynamic response could be quantified with Doppler ultrasound. Clinical onset of gastrointestinal disease was not seen after 4 days, indicating that the mucosal changes provoking these signs develop more slowly than the local vascular responses. The observed differences in the Doppler parameters between the regular and challenge diets may be a reflection of the difference between inactive versus active disease in these dogs.

Not only was a different postprandial response to food allergens shown in this study, but also a different preprandial response. The fasting RI and PI values were increased during the challenge period (day 2 and 4) compared to those obtained during the examinations on day 1, when the dogs were fed their regular diet. One possible mechanism is an overreaction of the vascular bed during the fasted

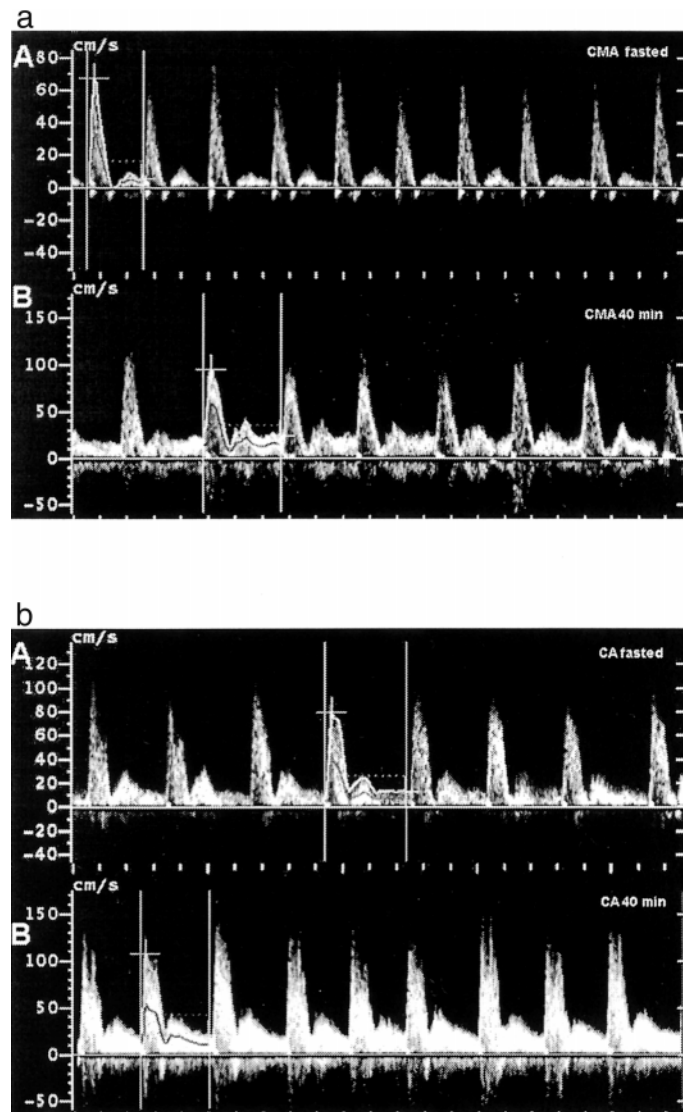


Fig 2. Spectral waveforms of (a) the cranial mesenteric artery (CMA) and (b) the celiac artery (CA) at fasting (t_0) and at 40 minutes post-prandially of 1 dog measured with the challenge diet at day 4. Note the marked increase in the diastolic part of the waveforms at 40 minutes compared to t_0 .

period resulting in exaggerated vasoconstriction. Mediators of this vasoconstriction have been discussed in the literature.^{41,42} Sustained production of large amounts of nitric oxide (NO) is induced in blood vessels by inflammatory stimuli as a result of the expression of the inducible form of NO-synthase (NOS-2). NOS-2 activity in blood vessels may protect tissues by virtue of the vasodilating, antithrombotic, and leukocyte adhesion inhibitory effects of NO.⁴¹ However, excessive production of NO in blood vessels is involved in circulatory failure occurring in systemic inflammatory reactions, and it may be cytotoxic for surrounding tissues. Cyclo-oxygenase-2 (COX-2) expression by endothelial cells of small mesenteric arteries in patients with Crohn's disease has been shown. Vasoconstrictor metabolites of COX are thought to be involved in the regulation of contraction of these small mesenteric arteries. Inflammatory cytokines, especially tumor necrosis factor- α , are

thought to be involved in the onset and perpetuation of mucosal lesions in Crohn's disease.⁴²

Another explanation for higher vascular bed resistance during the fasted state could be perivascular edema leading to an increase of the external pressure on the capillaries that then is overcome by postprandial (and perhaps exaggerated) vasodilatation. Although these mechanisms have been described for IBD, they also may play a role in food allergies. The exact mechanism of the vascular response to chronic enteropathies requires further investigation.

Elimination and challenge diets are current methods of identifying food allergens and such diagnostic trials often are lengthy.^{8,38} Also, a positive response to a food allergen requires clinical onset of disease in response to that allergen, and each allergen may have to be fed for a prolonged period of time before obtaining a result. The findings of this study show that a hemodynamic response to a food

allergen in a hypersensitive dog can be detected with Doppler ultrasound in the absence of clinical disease within a few days of feeding the food containing the allergen. It was shown previously that all dogs challenged in this study developed clinical signs after a longer challenge period.¹²

Both RI and PI infer to the resistance of the vascular region supplied by the measured vessel. Diastolic flow, being of low pressure and velocity, can be suppressed by various disease processes that cause an increase in peripheral resistance. For instance, perivascular cellular infiltrates or edema, intravascular obstruction (thrombosis), vasoconstriction, or external compression all potentially could compromise the total vascular diameter leading to a higher resistance in the affected vascular bed. This effect would lead to higher RI and PI values. Vasodilation of the arteriolar bed due to any possible reason would result in lowered RI and PI values because of a decrease in resistance of the vascular region.

Whether RI and PI are sufficient to describe the changes in arterial waveforms in healthy and affected dogs needs further investigation. The shape of the arterial waveform may hold information that a simple calculation of RI or PI cannot elucidate. For instance, we found that PI values decreased more than RI values. The RI only takes the end diastolic flow velocity into consideration and not the mean velocity. Therefore, the RI may not completely represent alterations in the arterial waveforms postprandially. In a pilot study, we extracted in addition to RI and PI other parameters from the CA and CMA waveforms of dogs with different chronic gastrointestinal diseases.⁴³ For example, mean diastolic velocity and diastolic notch ratios appear to have promise for more detailed evaluation of these waveforms and will need to be studied further.

In summary, significant differences in gastrointestinal hemodynamics in response to allergens in dogs with food hypersensitivity can be shown noninvasively with Doppler ultrasound. We conclude that this method may have potential as a diagnostic test for detecting food hypersensitivity and monitoring therapy. Doppler ultrasound investigations of gastrointestinal blood flow during digestion represent a way of studying functional changes in disease as opposed to purely morphologic abnormalities with gray-scale imaging. Future studies may involve the clinical application of this method and further investigation of different parameters in waveform analysis. Doppler ultrasound of the CA and CMA may provide an important tool in the noninvasive evaluation of the pathophysiology and monitoring of chronic enteropathies due to food intolerance in dogs.

Footnotes

^a Hill's Science Plan, Canine Maintenance, Hill's Pet Nutrition Inc, Topeka, KS

^b Siemens Sonoline Elegra ultrasound unit, Siemens Co Ltd, New York, NY

^c NCSS 2001, Number Cruncher Statistical Systems, Kaysville, UT

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