Manometric demonstration of duodenal/jejunal motor function consistent with the duodenal brake mechanism

Running title: Motor function of the duodenal brake

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Abstract:

Background

High resolution manometric studies below the stomach are rare due to technical limitations of traditional manometry catheters. Consequently, specific motor patterns and their impact on gastric and small bowel function are not well understood. This study used high resolution manometry to record fed state motor patterns in the antro-jejunal segment and to relate these to fasting motor function.

Methods

Antro-jejunal pressures were monitored in 15 healthy females using fiber-optic manometry (72 sensors at 1 cm intervals) before and after a high-nutrient drink.

Key Results

Post-prandial motility showed a previously unreported transition point 18.8 cm (range 13-28cm) beyond the antro-pyloric junction. Distal to the transition, a zone of non-propagating, repetitive pressure events (11.5 ± 0.5 cpm) were dominant in the fed state. We have named this activity, the Duodeno-Jejunal Complex (DJC). Continuous DJC activity predominated, but 9 subjects also exhibited intermittent clusters of DJC activity, 7.4 ± 4.9/hr, lasting 1.4 ± 0.55 min, 3.8 ± 1.2 min apart. DJC activity was less prevalent during fasting (3.6 ± 3.3 /hr; P = 0.04). 78% of fed and fasting state propagating antro-duodenal pressure events terminated proximally or at the transition point and were closely associated with DJC clusters.

Conclusions & Inferences

High-resolution duodeno-jejunal manometry revealed a previously unrecognised transition point and associated motor pattern extending into the jejunum, consistent with the duodenal brake previously only identified fluoroscopically. Timing of DJC activity suggests it is driven by chyme stimulating duodenal mucosal chemosensors. These findings indicate that the duodenum and proximal jejunum consists of 2 major functional motor regions.

Keywords

Small bowel motility; high-resolution manometry; duodenal brake; fibre optic manometry

INTRODUCTION

The duodenum is vital for digestive function, being where secretions are first mixed with acidic gastric chyme. Secretions are stimulated by duodenal mucosal sensing of components of chyme[1]. The effectiveness of duodenal chemical processing is evident from the rapid neutralisation of acidic chyme entering the duodenum[2, 3, 4].

Duodenal mucosal chemosensors also cause immediate modulations of gastric and pyloric motor function that moderate gastric emptying,[5, 6, 7] ensuring that the rate of emptying is matched to the speed of nutrient processing in the duodenum. Motor functions of the duodenum itself are also influenced by duodenal chemosensors[8, 9, 10]. Rao et al demonstrated fluoroscopically that intraduodenal infusions of sodium oleate, bile or hydrochloric acid caused almost instant flow-obstructive occlusion of the distal duodenum that did not occur with infusions of a normal saline/barium sulphate mixture. [9]. This flow-obstructive mechanism was dubbed the "duodenal brake", but the underlying mechanics remained undefined.

Traditional high resolution manometry catheters are not able to penetrate very far into the small bowel, hence we have used the larger span of 72 element high-resolution fibre optic manometry catheters to make 1 cm-spaced recordings of fed state and fasting pressures from the antrum into the region of the duodenal brake.

MATERIALS AND METHODS

Healthy Subjects

Studies were conducted at the Gasthuisberg campus, UZ Leuven, Belgium, after approval from its Medical Ethics Committee and the Federal Agency for Medicines and Health Products, Belgium. 15 female volunteers (26 ± 3 years, BMI between 18 and 25 kg/m2) gave

written consent and fasted for 12 hours prior to the study: none had any history of gastrointestinal diseases, abdominal surgery (appendicectomy allowed), psychiatric illnesses, nor use of drugs affecting the gastrointestinal tract or central nervous system.

Manometry Catheters

The catheters 3 mm diameter catheters each contained 72 1 cm-spaced fiber-optic pressure sensors. The devices were fabricated for investigational use only. Data from the catheter were acquired by a solid state fibre-optic spectrometer (FBG-scan 804D; FBGS International, Jena, Germany). Pressures were recorded by a custom-written LabVIEW© program (National Instruments, Texas, USA).

Study Protocol

With subjects seated, the catheter was passed transnasally until ~20 sensors were aborad of the lower oesophageal sphincter. With the subject supine, the catheter was passed through the pylorus under fluoroscopic guidance until the tip was at or beyond the duodeno-jejunal flexure The catheter was then taped to the nose. Abdominal X-rays (Fig 1) documented sensor locations at study start and completion.

Subjects were studied semi-reclined. Fasting recordings were continued until 2 phase III periods of the migrating motor complex (MMC) were recorded, or for a maximum of 5 hours. Subjects then ingested a standard 200 ml nutritional drink (Vanilla Multifibre Nutridrink, Nutricia; 480 kcal, 42% carbohydrate, 39% lipid, 3% fiber). Fed-state activity was then recorded for 60 - 120 min.

Analysis of manometric recordings

Pressures were analysed both manually with software (PlotHRM, written in Matlab©, The MathWorks, Massachusetts, USA) and JavaTM (Sun Microsystems, California, USA) and with an in-house developed automated system (see below)[15].

Fed-state pressures were analysed in detail for 60 min following the drink intake. These were compared to fasted pressure patterns during 30 min prior to the drink. Definite phase III MMC episodes that occurred during the fasted period in 7 subjects were excluded from analysis (see Discussion) and an equivalent epoch prior to the phase III substituted.

Pressure sensor locations were determined from characteristic frequencies and/or patterns of pressures of the lower esophageal sphincter, antro-pyloric junction and duodenum. Antro-pyloric junction position was taken as the most aborad point at which the underlying frequency was 3 cycles per minute (cpm) (Fig 1B).

Manual pressure event analysis

Propagation was confirmed if a pressure event peak occurred in 3 or more adjacent channels (i.e., ≥2 cm), each with a trough-to-peak amplitude of at least 5 mmHg, and if the up-stroke of each adjacent pressure wave commenced during the pressure event in an adjacent channel[11]. Direction of travel, velocity (cm/s), extent (cm), and peak amplitude (mmHg) of propagating pressure events were scored and their origins were recorded as either antro-pyloric, duodenal loop or duodeno-jejunal (see below).

Automated measurements of duodenal and jejunal pressure events

The automated analysis surveyed the frequencies and amplitudes of pressure events at each recording site. As previously described[12] base-line drift, respiration, coughs and straining artefacts were removed from the manometry traces.

The frequencies of pressure events at each sensor were detected using a wavelet transform [13]. The root-mean-square amplitude over time was derived for the duodenal loop and duodeno-jejunal regions (see below) during fasting and after the drink. The wavelet transform was set up to detect physiological frequencies between 4 -16 cycles per minute (cpm) as this

was the frequency range over which the majority of activity occurred. These steps produced curves which represented wavelet amplitudes over all of the assessed frequencies for each of the subjects (Fig 2).

Spatial referencing of pressure events

Fed and fasting patterns of duodenal and proximal jejunal pressures revealed a previously undescribed transition point of motor patterns in the distal duodenum. We used this point to divide the duodenum and proximal jejunum into two functional regions, as described below.

Statistical comparisons:

Propagating pressure events: Comparisons of numbers, amplitude, velocity, extent of propagation for propagating pressure waves before and after the nutrient drink were made with a nonparametric Wilcoxon matched-pairs signed rank test. Comparisons between different propagating motor patterns used a Mann-Whitney test (GraphPad Software, Inc., La Jolla, CA, USA).

Statistical comparison of multiple frequencies of pressure events between the different regions, before and after the meal used Bayesian analysis[14,15]. This was categorised by region (‘duodenal loop’ and ‘duodeno-jejunal’, defined in the results) and period (‘fasted’ and ‘fed’)[16]. The probability distribution of the statistical model's parameters was calculated using the Stan software[17].

RESULTS

Duodenal intubation succeeded in all subjects. Within the first 5 hours, phase III MMC activity occurred twice in 7 subjects, once in 6 and not at all in 2. The nutrient drink was given 238 ± 85 min (range 94 – 300 min) after the start of fasting recordings.

Division of the duodenum and proximal jejunum into two major functional regions

In all 15 subjects the fed-state recordings revealed a clear transition point of motor patterns in the distal duodenum, beyond which non-propagating pressure events at a frequency of 9-12/min extended aborally across all sensors (Fig1). We have named this motor pattern the Duodeno-Jejunal Complex (DJC). The duodenum orad to the transition point was named the Duodenal Loop (DL) region and the region aborad to the transition point, the Duodeno-Jejunal (DJ) region. The transition point was also evident during fasting (Fig 3, see below). When catheter migration during the meal was accounted for, the position of the transition point position in fasted and fed states did not vary within individuals.

The average distance of the transition point from the antro-duodenal junction was 18.8 ± 3.7cm (range 13 – 28cm). In three subjects, the depth of insertion of the catheter did not extend significantly beyond the transition point for DJ region motility analysis, though the transition point could be recognised. Accordingly, the data on motor patterns in the DL and DJ regions were from 15 and 12 subjects respectively.

Fed-state duodeno-jejunal region activity

DJC activity was the dominant fed-state DJ region motor pattern. This had a mean frequency of 11.5 ± 0.5 cpm (Fig 2E). There was no clear propagation between the individual DJC pressure events at adjacent recording points (Figs 4B, 5B).

In 9 subjects, DJC activity became the dominant pattern within 90s of starting the nutrient drink. In the remaining 3 subjects, duodenal phase III-like activity [18,20] occurred within 45-90s of starting the nutrient drink. This activity, which persisted for 5 – 15 min, was followed by an 8 – 11 min quiescent period after which DJC activity commenced.

Once DJC activity commenced, it persisted throughout the one hour fed-state recording. In 9 of 12 subjects, at 12.3 ± 8.4 min after the nutrient drink, discrete clusters of more intense DJC activity were also observed (Figs 4A,B). In 8 subjects these clusters occurred over ~25

minutes, followed by continuous DJC activity. In 1 subject, clustered DJC activity continued for the full fed-state recording (Fig 4A). Clusters occurred at 7.4 ± 4.9 per hr, with an interval between them of 3.8 ± 1.2 min and lasted 1.4 ± 0.55 min. The frequency of pressure events within fed-state clusters was 10.8 ± 0.8 cpm. These clusters extended to the most aborad pressure sensor over a minimum of 23.5 ± 2.9cm aborad from the transition point. Some DJC clusters were static, but in most, their orad margin moved aborad at variable rates (0.8 ± 0.5 cm/s; Range 0.2 – 1.9 cm/s) (Fig 4B).

Fed-state motor function in the duodenal loop region.

In the DL region, after the nutrient drink, pressure events in individual channels occurred at frequencies between 6 – 12 cpm (Fig 2D). However, while there were short periods of localised 10-12 cpm events they were significantly less frequent and extensive compared to DJC activity (Fig 2 E &F). DL region activity (Tables 1, 2) was dominated by events that propagated varying distances, predominantly in an aborad direction from the antropyloric and proximal DL regions at a rate of 4-6 per min (Fig 3 & 4C), with more than half extending at least 10 cm (Table 1). Orad propagating and synchronous events in the DL region accounted for 6% and 17% of events respectively.

Relationships between fed-state motor function in the duodenal loop and duodeno-jejunal regions

Of the 1760 aborad propagated pressure events originating in the antropyloric or DL regions, 78% did not cross the transition point; the events that did had a greater peak pressure amplitude than those that terminated before or at the transition point (Table 2, $p = 0.007$).

Overall, 80% of all DJC activity clusters were preceded within 30 sec by usually vigorous (561.3 ± 162.2 mmHg) antro-pyloric pressure events. Clustered DJC activity also occurred in

the absence of preceding antro-pyloric events in 2 subjects. Vigorous antro-pyloric events also occurred during continuous DJC activity (Fig 5A).

Fasting compared with fed-state motor function

Following the identification of the fed-state DJC, similar DJC activity was also recognized during fasting, but it was less prevalent and of lower amplitude compared to the fed-state (Figs 2B & H, Fig 3). While short bursts of fasting DJC activity were seen in single or several adjacent channels, there were no prolonged episodes (>3min). Clusters of DJC activity occurred during fasting in 8 subjects at 3.6 ± 3.3 /hr, less than in the fed state (7.4/hr; P = 0.043). Fasting clusters had a significantly shorter duration (34.1± 7.3 sec; P = 0.02) and lower frequency of their individual regular pressure events (7.2 ± 1.5/min; P = 0.01), than fed-state clusters. Fasting clusters frequently did not extend aborad over all of the DJ region sensors (Fig 3A). Fasting DJC clusters were all preceded by vigorous antro-pyloric pressure events (582.4 ± 213.3 mmHg) and long (>10cm) aborad- propagated events in the DL region (Fig 3A). The overall frequency, amplitude, velocity and extent of propagating pressure waves in and beyond the duodenal loop region did not differ significantly between the fasted and fed states (Tables 1,2).

DISCUSSION

We propose that DJC activity is the motor mechanism of the “duodenal brake” in humans. Our data show that this is a fundamental physiological mechanism as it is active during gastric emptying of even the modest nutrient intake used in this study. The patterns observed yield insights on how the proposed brake activity relates to gastric and duodenal motor function orad to the distal duodenum.

The two major new findings are firstly, that the motility of the duodenum and proximal jejunum can be differentiated into two physiologically distinct segments, the Duodenal Loop

(DL) and Duodeno-Jejunal (DJ) regions. Secondly, at the orad margin of the DJ region in the distal duodenum, there was a sharp point of transition (Figs 1,3,4,5) to a previously undescribed pressure pattern that we have named the Duodeno-Jejunal Complex (DJC).

DJC activity was most prevalent after the nutrient drink compared to fasting and extended into the DJ region more than 20 cm aborad from the transition point. The spatiotemporal pattern of the pressures of DJC activity is consistent with it impeding emptying of content from the DL region (see below).

The proposal that DJC activity retains digesta in the DL region is consistent with the observations in healthy subjects by Rao et al[9] who showed fluoroscopically that infusions of bile, lipid and acid into the duodenal loop caused immediate and sustained closure of the most distal part of the duodenal lumen by what they called the "duodenal brake".

Pancreatic and biliary secretions empty into the Duodenal Loop region through the ampulla of Vater 7-10 cm aborad from the pylorus. This central position in the DL region, (as defined in this report), seems to be well-suited to support a rapid onset of digestion by achieving effective mixing of these secretions with chyme when they are retained by DJC activity. The transition point we identified between the DL and DJ regions, which was the most orad position of the zone of DJC activity, was 18.8 ± 3.7 cm aborad from the antro-duodenal junction. This distance accords with the most orad position of the zone of duodenal luminal closure observed fluoroscopically by Rao et al [9]. Rao et al used duodenal manometry, but their recording points only extended ~12cm into the duodenum, well short of the DJC activity we observed. Definitive testing whether DJC activity impedes flow will need concurrent imaging and high resolution manometric studies.

Apart from the anatomical concordance of DJC activity with the duodenal brake [9], there is persuasive indirect evidence that DJC activity is flow-impeding: the frequency and spatial

patterning of the individual pressure events in DJC activity closely resembles phase III MMC activity, except that DJC activity is not preceded by duodenal loop phase III motor activity, is anchored to the DJ region and does not show the stereotypical aborad migration which underlies the small intestine lumen-sweeping mechanics of phase III MMC[19]. Fluoroscopy and impedance monitoring have shown that the lumen is occluded continuously in segments of duodenum or proximal jejunum encompassed by the phase III MMC[20]: this is likely to be the also the case for DJC activity, given its close similarity. Purely on manometric grounds, the frequency of DJC activity is so high and the duration of the pressure "valley" between each pressure event is so brief (Fig 5) that the lumen is unlikely to fill with any content between individual events, especially when DJC activity extends for many centimeters. Also, vigorous propulsive, aborally propagated DJ region pressure events that could overcome the resistance from DJC activity are uncommon during DJC activity (Figs 1,3,4,5, Table 2).

Given our data and those of Rao et al[9] our hypothesis is that the duodenal brake mechanism actively impedes emptying of chyme from the DL region until its pH has been largely neutralised and it has been thoroughly mixed with and partially processed by the secretions delivered to the duodenal loop. We propose that, with time, these functions alter the chemistry of the duodenal content to the point that it no longer causes major stimulation of DJC activity by duodenal loop chemosensors, allowing it to be delivered into the upper jejunum.

The timing of periods of DJC activity supports the concept that this is modulated by signaling from duodenal chemosensors as the vigor, luminal extent and prevalence of fasting DJC activity was less than in the fed state (Figs 2,3,). Secondly, clusters of fed state DJC activity were strongly associated with propagated antro-duodenal events (Tables 1,2) known to cause delivery of pulses of chyme into and along the duodenum in the fed state [22,23,24]. This

association is best explained by these pulses of nutrients causing surges of duodenal mucosal chemosensor signaling. The long periods of continuous fed-state DJC activity seen in 3 subjects could be explained by a relatively constant and slow flow of chyme into the duodenum with a lower, but continuous, stimulus to chemosensors and DJC activity. Predominantly pulsatile or non-pulsatile gastric emptying are known to occur, with considerable variations over time and among individuals[4].

The primary aim of our analysis of the pressure recordings was to evaluate fed-state pressure patterns. The recognition of DJ region pressure patterns in the fed state that are best explained by duodenal brake motor activity prompted us to also evaluate 30 minutes of the fasting recordings in each subject for occurrence of DJC activity and the presence of a transition zone. This tested whether increased DJC activity was associated with entry of nutrient chyme into the duodenum: this analysis was complicated by the need to exclude periods of phase III activity in the antroduodenal segment. It is not feasible nor directly relevant to the aims of this report to include a detailed assessment of fasting motor activity in this report, but this will be the subject of a second evaluation. In the light of the paragraph immediately below, it would seem worth comparing presence, extent and vigor of fasting DJC activity during phases I and II of the MMC cycle.

The relatively brief DJC clusters recorded during fasting may appear to refute the proposal that these are stimulated by duodenal chemosensors. However, episodic duodenal acidification occurs during fasting, in association with the highly expulsive interdigestive phase II antro-pyloric pressure events[2, 4] and it was these events that we found to be strongly associated with fasting DJC activity clusters (Fig 3). That the duodenal brake is potently activated by duodenal acidification alone was shown by Rao et al[9].

The stimulation and modulation of DJC activity during fasting and gastric emptying of the modest caloric intake provided by the nutrient drink indicates that the duodenal brake is

active under normal physiological conditions. This refines the findings of Rao et al [9] whose observations might be interpreted as revealing a mechanism possibly triggered only by duodenal chemical "overload", since it is unclear if the infusate stimuli they delivered directly to the duodenum were within the physiological range for the duodenal luminal environment.

Rao et al[9] reported stimulation of the duodenal brake within seconds of the start of the duodenal delivery of infusates, consistent with our finding that clusters of DJC activity started within seconds of motor events previously shown to deliver pulses of gastric content from the stomach to the duodenum[21, 22]. The rapidity of the response of the duodenal brake to duodenal chemical stimuli can only be explained through neural mediation. Pharmacological analysis, antral field stimulation[23] and proximal duodenal transection[24] indicate that ascending intramural nerves are the major pathway for the pyloric stimulatory and antral inhibitory effects of stimulation of duodenal chemosensors. The present study suggests that duodenal chemosensors also signal along descending duodenal intramural pathways to modulate motility and specifically DJC activity.

The episodes of phase III-like activity seen in some subjects following consumption of the nutrient drink are of uncertain significance. These are clearly not DJC activity, as they started in the orad part of the DL region and propagated down the duodenum into the jejunum in the same orderly manner as true Phase III MMC activity. Rao et al[9] also noted stimulation of duodenal 'phase III-like activity' with some episodes of duodenal infusion. Other intraduodenal infusions[6, 8, 9], cold stress[25] and systemic hyperglycaemia produced by an intravenous dextrose infusion[18] have also been found to trigger similar activity.

Given that DJC activity had not been recognized prior to this study, a dose-response study was not possible. By removing the variablility of gastric emptying rates, future duodenal infusion-based studies would better define control of DJC activity by components of the

duodenal content and give better insight into whether the absence of clustered fed-state DJC activity seen in 3 of our subjects was due to predominantly non-pulsatile gastric emptying.

The absence of any imaging data that examine the mechanics of DJC activity could be seen as the second major limitation of the present study, but our analysis, and that of Rao et al[9], provides strong indirect support that DJC activity impedes flow. The outcomes of the present study now provide the guidance needed for design of ethical imaging studies of DJC activity in the future.

Confirmation of the existence and physiological importance of the duodenal brake may present opportunities for less morbid types of surgery of the stomach and duodenum. Perturbed DJC activity may also contribute to troublesome slow gastric emptying in some patients that might be addressable by interventions targeting DJC activity. Finally, since the rate of delivery of glucose into the upper jejunum, beyond the region of the DJC, is likely to have a major effect on the rate of glucose absorption, it is an intriguing question whether aberrant DJC activity could contribute to impaired glucose tolerance.

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Table 1. Characteristics of aboral propagating motor patterns originating in the antro-duodenal or duodenal loop region before and after nutrient drink.

	Extent (cm)	Count / hr	Velocity (cm/s)	Amplitude (mmHg)
Fed State	**≤5**	11.5 ± 11.1	3.4 ± 1	25.1 ± 7.1

	6-9	49.5 ± 39.1	3.2 ± 0.7	26.3 ± 4
	10-14	38.4 ± 32.1	3.5 ± 0.9	28.1 ± 4.9
	15-19	21.2 ± 18.7	3.2 ± 0.9	33.9 ± 7.7
	≥20	13.4 ± 16.2	2.6 ± 1.0	41.4 ± 5.7
Fasted State	**≤5**	5.8 ± 6.8	3.1 ± 1.5	27.8 ± 11.6
	6-9	31.7 ± 20.4	3.5 ± 0.7	28.7 ± 6.1
	10-14	32.5 ± 24.1	3.9 ± 1.0	32.2 ± 5.2
	15-19	20.3 ± 26.1	3.6 ± 1.2	40.2 ± 7.6
	≥20	12.2 ± 21.1	3.3 ± 1.0	43.6 ± 7.7

Table 2. The site of origin, count, amplitude and velocity of propagating motor patterns that terminate at or prior to the transition point and those that propagated over the transition point (grey shaded rows).

	Fed State			**Fasted State**		
Site of origin – termination region	**Count / hr**	**Amplitude (mmHg)**	**Velocity (cm/s)**	**Count/hr**	**Amplitude (mmHg)**	**Velocity (cm/s)**
A - DL	0.4 ± 0.9	37.2 ± 16.5	3.5 ± 1.3	2.2 ± 3.7	47.2 ± 7.2	4.1 ± 0.8
A - DJ	0.3 ± 0.9	46.8 ± 1.0	3.6 ± 1.4	1.0 ± 1.8	56.9 ± 9.0	3.0 ± 1.1
DL - DL	40.8 ± 23.8	27.0 ± 4.2	3.5 ± 1.0	33.8 ± 27.7	32.1 ± 4.3	3.7 ± 0.9
DL - DJ	10.2 ± 11.4	34.1 ± 6.0	3.4 ± 0.8	8.4 ± 7.8	41.0 ± 3.8	3.5 ± 1.2

A = Antro-duodenal region

DL = Duodenal loop region

DJ = Duodeno-jejunal region

Figure Legends

Fig 1. (A) X-ray image of the fibre-optic manometry catheter *in situ.* (B) Manometry trace, presented as a spatiotemporal color plot, recorded after the nutrient drink. The differing manometric patterns recorded along the catheter illustrate the functional specialisation of the antropyloric, duodenal loop and duodeno-jejunal regions.

Fig 2. Bayesian analysis of pressure wave frequency in the duodenal loop (DL) region (A & D) and the duodeno-jejunal (GJ) region (B & E), both before (left column) and after (middle column) a meal. The end of each column (C, F) compares mean pressure wave frequencies between the DJ and DL region. When the thick black line appears above the hatched line, activity is significantly greater in the DJ region, below the hatched line the activity is significantly greater in the DL region. The end of the two rows (G & H) compares data between the fed fasted states in the in the two small bowel regions. The thick black line above the hatched line indicates a significant increase in response to a meal.

Fig 3. Fasting and fed-state tracings in the same subject. (A). Fasting powerful phase II antral and propagated duodenal loop region events and brief, mainly localised clusters of DJC activity in the duodeno-jejunal region. (B). After the nutrient drink, there is aborad movement of the manometric catheter and more vigorous, almost continuous and more extensive DJC activity.

Fig 4. (A). Fed-state clustered DJC activity over 26 min, which is expanded in B to show the variable spatial patterns of DJC activity (hatched red arrows). (C) shows antral and duodenal loop region pressures which demonstrate aboral propagation (black arrow)

Fig 5. (A) Continuous fed-state DJC activity. (B) A highly expanded time base showing the non-propagated pattern of DJC pressure events.