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ORIGINAL ARTICLE

Abnormal total ejection isovolume index as early noninvasive marker of chronic rejection in heart transplantation*

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Summary

Abnormally high myocardial performance index (MPI) is a Doppler-derived marker of combined systolic and diastolic left ventricular (LV) dysfunction. To identify early stage allograft dysfunction by MPI, we studied 154 long-term heart transplantation (HT) recipients (131 male, aged 51 ± 13 years at HT, mean follow up 8.4 ± 3.5 years), with normal left ventricular ejection fraction (LVEF) and free from acute rejection (AR), and 25 normals (13 male, aged 39 ± 16 years). Rejection score (RS) on endomyocardial biopsy was calculated in the first year. MPI was prolonged (0.45 ± 0.18 vs. 0.28 ± 0.10, $P = 0.0001$) in patients and directly related with mean time from HT ($P = 0.001$), higher cumulative dosages of cyclosporine at 3 months ($P = 0.01$), 6 months ($P = 0.03$), 1 year ($P = 0.02$), 3 years ($P = 0.04$) and with cumulative dosage of methylprednisolone at 1 year ($P = 0.002$). The index was inversely related with mean age at HT ($P = 0.002$) and tended to be directly related with RS at 1 year ($P = 0.05$). Thus, MPI is abnormal in long-term HT recipients with normal LVEF. Its direct relation with time from HT as well as immunosuppressive load suggests an early stage of graft dysfunction because of chronic rejection. Extended prospective studies are warranted to clarify its potential role as a negative prognostic marker in HT.

Introduction

Heart transplantation (HT) is a definitive therapy for end-stage heart failure [1]. Although acute (AR) and chronic allograft rejection (CAV) represent major causes of morbidity and mortality in HT, early noninvasive echocardiographic markers are lacking. Besides AR and CAV, other factors may adversely affect both systolic and diastolic left ventricular (LV) function of the transplanted heart [2,3]. During AR, systolic and diastolic dysfunction has been demonstrated by hemodynamic measurements [2,3] as well as echocardiography [2,4–6], and it has been shown that it is reversed by rejection therapy [3,6]. In contrast, myocardial function of the long-term nonrejecting allograft, and the factors influencing it, have not been fully elucidated. Recently, the myocardial performance index (MPI), a new Doppler-derived index of combined systolic and diastolic myocardial performance, has been introduced [7]. It is derived as a composite ratio of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) to the ejection time (ET). MPI is independent of

LV geometry, heart rate, and blood pressure [8] and it has been shown to be of prognostic value for patients with cardiac amyloidosis [8], dilated cardiomyopathy [9], and congestive heart failure [10]. The aim of this study was to assess the clinical utility of the MPI as early noninvasive marker of long-term cardiac allograft dysfunction.

Patients and methods

Study patients

This was a prospective study of 154 long-term HT recipients (131 male, aged 51 ± 13 years at HT, mean follow up 8.4 ± 3.5, range: 2.2–16.4) with preserved systolic function and without atrial fibrillation or atrioventricular block. Pre-HT diagnosis was: dilated cardiomyopathy in 72 patients (47%), coronary artery disease in 57 (37%), valvular heart disease in 14 (9%), other in 11 patients (7%). Donor age was 33 ± 14 years (range: 9–63), total ischemia time 154 ± 53 min.

The HT recipients were treated with antithymocyte globulin for the first 3–5 days, cyclosporin A (CsA) and azathioprine (Aza) (double therapy), or with CsA, Aza and oral prednisone (PDN; triple therapy) as detailed [11]. Mean donor age were 33 ± 14 years. All patients were asymptomatic (New York Heart Association functional Class I). Our control group included 25 normal subjects (13 male, aged 39 ± 16 years) with no symptoms suggestive of cardiovascular disease, normal physical, electrocardiographic, and two-dimensional (2D)/Doppler echocardiographic findings. The study was approved by the Human Research Committee at our University. All patients and control subjects gave informed consent to the study.

Acute rejection scores and cumulative immunosuppressive load

Acute graft rejection was monitored by endomyocardial biopsy [11] and graded according to the ISHLT nomenclature [12]. Acute rejection (AR) episodes, defined as grade >2, were treated [11]. A rejection score (RS) was assigned based on a modification of the ISHLT grading as follows: 1A = 1, 1B = 2, 2 = 3, 3A = 4, 3B = 5, and 4 = 6 [11,13]. The following scores were calculated for each patient: RS in the total follow up (TRS); RS in the 1st year (RS 1 year); TRS including only severe grades (sev TRS; ≥3A); first year RS including only severe grades (sev RS 1 year). All scores were normalized for the number of biopsies taken in each patient.

Cumulative doses (mg/kg) of CsA, Aza, PDN, and methylprednisolone (MethPD) at 3, 6, and 12 months, and cumulative total steroid load in the first year were calculated. Cumulative PDN load of each patient in the first year (PDN 1 year) was calculated in mg/kg, as well as cumulative MethPD (1 year), and total steroid load (TotCORT: 1 year = PDN 1 year + MethPD 1 year), as described [11,13].

Echocardiographic examination

Complete M-mode, 2D and Doppler echocardiograms were performed with a Hewlett-Packard 5500 Sonos system (Andover, MA, USA) using a 2.5-MHz combined imaging and Doppler transducer. A parasternal short-axis view at the mid-LV level was used for the measurements of LV end-systolic and end-diastolic dimensions. Left ventricular ejection fraction (LVEF) was measured using Simpson's method. The mitral inflow velocity pattern was recorded from the apical four-chamber view with the pulsed-wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole. The LV outflow velocity pattern was recorded from the apical five-chamber view (or apical long-axis view) with the pulsed-wave Doppler sample volume positioned just below the aortic valve.

Doppler measurements

All echo/Doppler parameters were measured from monitor recordings. Five consecutive beats were measured and averaged for each measurement. Doppler time intervals were measured from mitral inflow and LV outflow velocity time intervals (Fig. 1). The interval 'a' from the cessation to the onset of mitral inflow is equal to the sum of ICT, ET, and IRT. LV ET 'b' is the duration of LV outflow velocity profile. Thus, the sum of ICT and IRT was obtained by subtracting 'b' from 'a'. The index of combined LV systolic and diastolic function (the sum of ICT and IRT divided by ET) was calculated as (a − b)/b [7]. In addition, IRT was measured by subtracting the interval 'd' (between the R-wave and cessation of LV outflow) from the interval 'c' (between the R-wave and the onset of mitral inflow) (Fig. 1). ICT was calculated by subtracting the IRT from a − b (Fig. 1).

Statistical analysis

Data were analyzed with SPSS software version 10.1 (SPSS, Inc., 1999, Chicago, IL, USA). Results are expressed as mean value ± SD, unless otherwise specified. Unpaired Student's *t*-test was used for comparisons of mean values. The ordinal data were analyzed by chi-square test. *P*-values <0.05 were considered statistically significant. Pearson test was used to correlate paired data.

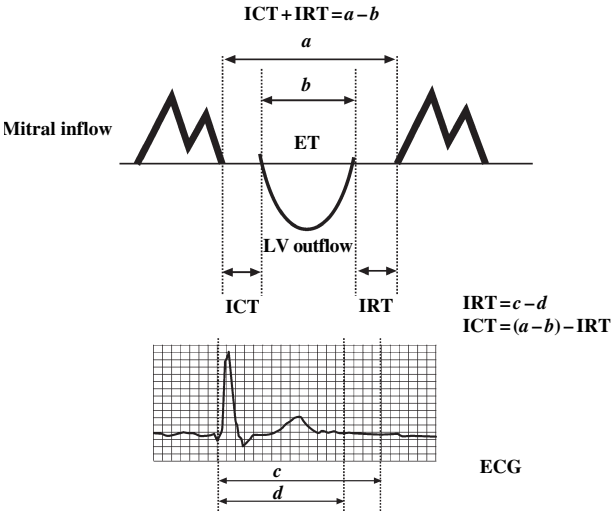

Figure 1 Measurements of Doppler time intervals. MPI (ICT + IRT/ET) is derived as (a – b/b), where 'a' is the interval between cessation and onset of the mitral inflow, and 'b' is the ET of the LV outflow. IRT is measured by subtracting the interval 'c' between the R-wave (electrocardiogram, ECG) and the cessation of LV outflow from the interval 'd' between the R-wave and the onset of mitral inflow. ICT is derived by subtracting IRT from a – b. MPI, myocardial performance index; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time; LV, left ventricular.

Results

Baseline features in the study groups

Baseline clinical and echocardiographic findings in patients and controls are shown in Table 1. HT patients were older and were more frequently of male gender. Body mass index (BMI), heart rate (HR), and mass/volume (M/V) ratio were higher in patients. Conversely, mean LV end-diastolic volume (LVEDV), LVEF, and systolic (SBP) and diastolic blood pressure (DBP) were similar.

Table 1. Clinical and general echocardiographic data.

	Controls ($n = 25$)	HT recipients ($n = 154$)	*P*-value
Age	39 ± 16	51 ± 13	0.001
Gender (male/female)	13/12	131/23	0.0001
BMI	24 ± 4	28 ± 14	0.01
HR (beats/min)	78 ± 14	87 ± 11	0.001
SBP (mmHg)	135 ± 22	144 ± 16	0.06
DBP (mmHg)	86 ± 11	90 ± 9	0.08
LVEDV (ml/m^2)	57 ± 10	61 ± 15	0.09
LVEF (%)	64 ± 6	62 ± 8	0.09
M/V ratio	1 ± 0.1	1.14 ± 0.2	0.0001

HT, heart transplantation; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDV, mean left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; M/V, mass/volume ratio.

Doppler measurements

Figure 2 illustrates an example of MPI calculation in a normal subject and in a HT recipient. Doppler measurements are shown in Table 2. Peak early (E) and late (A) diastolic filling velocities were shorter in HT recipients (75 ± 23 vs. 85 ± 21 cm/s and 39 ± 13 vs. 60 ± 13 cm/s respectively); accordingly E/A ratio was increased in patients (2.1 ± 1 vs. 1.4 ± 0.3). ICT was prolonged (60 ± 44 vs. 21 ± 20 ms, $P = 0.0001$), whereas ET was shortened in patients compared with normal controls (279 ± 29 vs. 310 ± 24 ms respectively, $P = 0.0001$; Fig. 3); IRT was similar in HT recipients and normals (70 ± 16 vs. 72 ± 19 ms respectively, $P =$ NS). Thus, the index combining these variables, easily obtained in all study subjects, ranged from 0.09 to 1 and was significantly higher in HT recipients than in normal subjects (0.45 ± 0.18 vs. 0.28 ± 0.1 respectively, $P = 0.0001$; Fig. 4).

Correlations of Doppler index

Correlations are shown in Table 3. MPI was inversely related to age at HT ($r = -0.249$, $P = 0.002$). Conversely MPI was directly related to mean time from HT ($r = 0.263$, $P = 0.001$) cumulative doses of CsA at 3 months ($r = 0.215$, $P = 0.01$), 6 months ($r = 0.180$, $P = 0.03$), 1 year ($r = 0.202$, $P = 0.02$), and 3 years ($r = 0.196$, $P = 0.04$) as well as to MethPD 1 year ($r = 0.259$, $P = 0.002$). Finally, the index also tended to be inversely related with donor age ($r = -0.155$, $P = 0.05$) and directly with CsA at 2 years ($r = 0.181$, $P = 0.05$) and RS 1 year ($r = 0.156$, $P = 0.05$).

Discussion

Our study shows for the first time that MPI, a reliable predictor of combined systo-diastolic dysfunction in heart failure [8–10], is abnormal in long-term HT recipients with preserved systolic function, e.g. LVEF > 50%. This finding provides new evidence in support of early global cardiac allograft dysfunction in the long term. In fact, MPI represents an ideal test for evaluating cardiac performance, as it gives a noninvasive, integrated assessment of systolic and diastolic LV function. In addition, MPI does not artificially uncouple systolic from diastolic function, is independent of ventricular loading conditions and is reproducible at serial follow up [7]. Furthermore, MPI is independent of HR and blood pressure [8]; this is an advantage in assessing allograft function in HT patients,

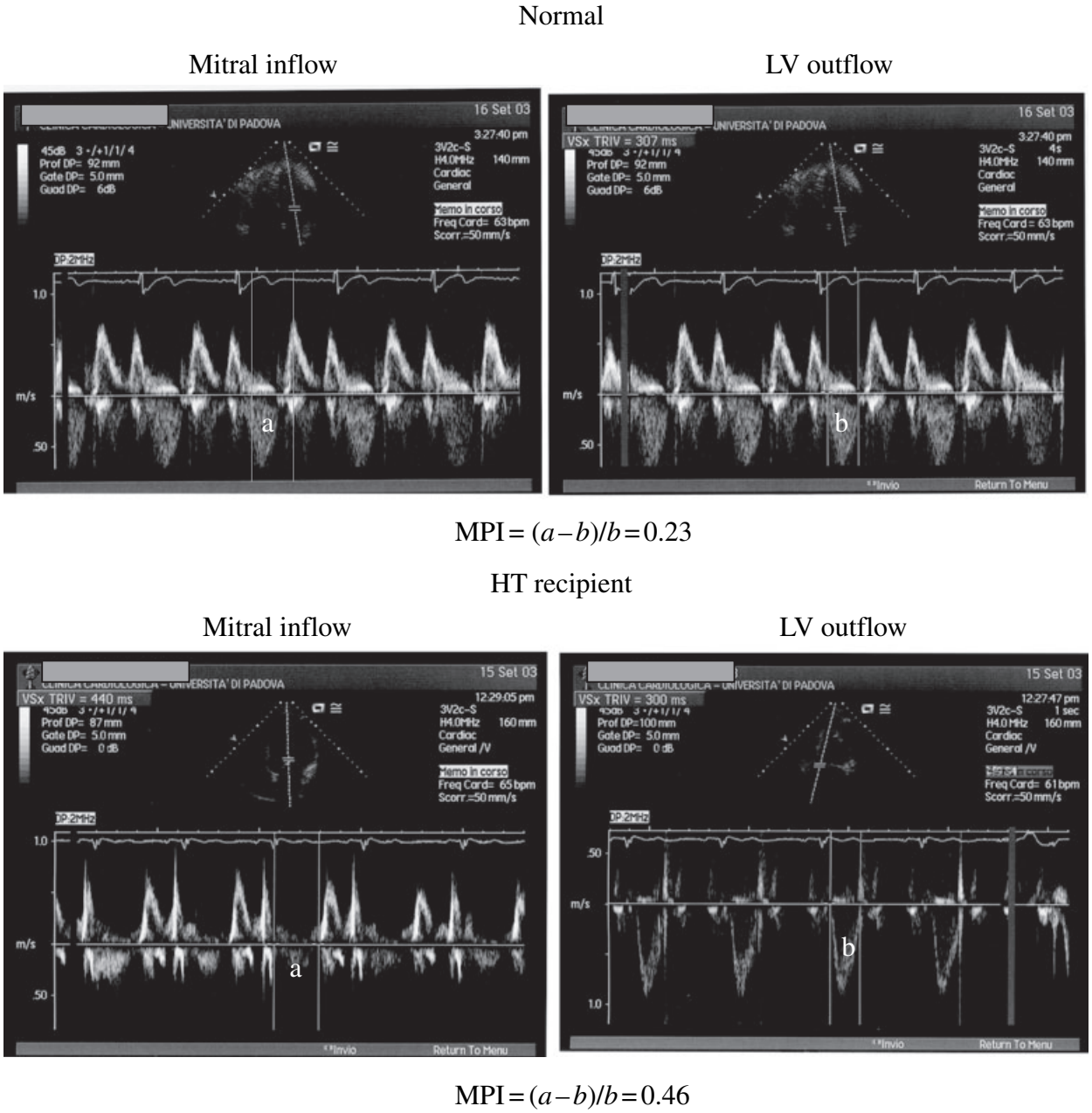

Figure 2 Pulsed-wave Doppler of mitral inflow and LV outflow in a normal 38-year-old male subject (LVEF = 61%) and a 40-year-old male HT recipients (LVEF = 60%). The value of the MPI is 0.23 in the normal subject and 0.46 in the HT recipient. LV, left ventricular; LVEF, left ventricular ejection fraction; HT, heart transplantation; MPI, myocardial performance index.

as they are almost invariably tachycardic and hypertensive [1]. In keeping with this, our patients had higher HR and M/V ratio compared with normal controls.

Our correlative data showed that MPI was directly related to mean time from HT and cumulative doses of CsA and steroids. In addition, MPI tended to be higher in patients with higher RS 1 year. Our interpretation of the correlation between abnormal MPI and immunosuppressive load is twofolds. First, as patients with higher CsA load had higher RSs, the association of high CsA load with impaired LV function may, at least in part, reflect higher immunosuppressive therapy given to patients with a high rejection frequency. Secondly, higher CsA load may identify patients who are poor absorbers of the drug and are therefore at higher risk of AR. Trough levels, average daily dose, and cumulative load of CsA give

Table 2. Doppler-derived variables.

	Controls ($n = 25$)	HT recipients ($n = 154$)	*P*-value
E (cm/s)	85 ± 21	75 ± 23	0.04
A (cm/s)	60 ± 13	39 ± 13	0.0001
E/A ratio	1.4 ± 0.3	2.1 ± 1	0.0001
ET (ms)	310 ± 24	279 ± 29	0.0001
ICT (ms)	21 ± 20	60 ± 44	0.0001
IRT (ms)	72 ± 19	70 ± 16	0.6
MPI	0.28 ± 0.1	0.45 ± 0.18	0.0001

E/A, ET, ICT, IRT, MPI MPI, myocardial performance index; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time; HT, heart transplantation.

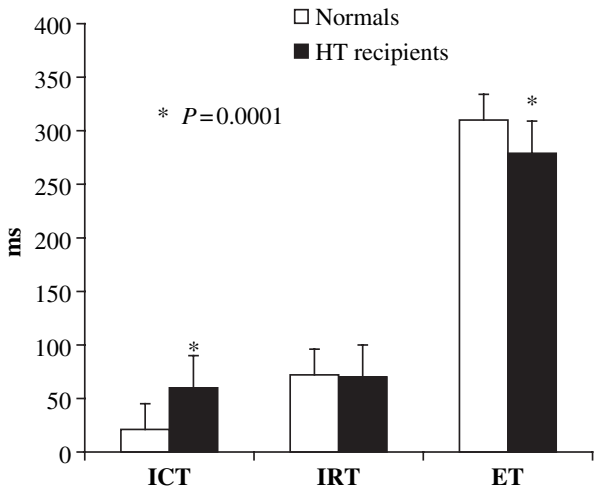

Figure 3 Comparison of Doppler time intervals between normal subjects and HT recipients. ICT was significantly prolonged, whereas left ventricular ET was significantly shortened in HT recipients compared with that in normal subjects. HT, heart transplantation; ICT, isovolumetric contraction time; ET, ejection time.

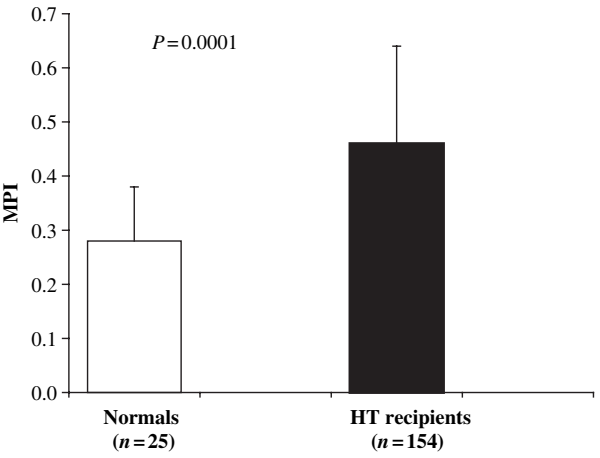

Figure 4 Comparison of the myocardial performance index (MPI) between normal subjects and heart transplantation (HT) recipients. The MPI is significantly prolonged in HT recipients compared with that in normal subjects.

Table 3. Correlation between MPI and clinical variables.

	r-Value	*P*-value
Age at HT	−0.249	0.002
Donor age	−0.155	0.05
Follow up	0.263	0.001
CsA at 3 months	0.215	0.01
CsA at 6 months	0.180	0.03
CsA at 1 year	0.202	0.02
CsA at 2 years	0.181	0.05
CsA at 3 years	0.196	0.04
MethPD 1 year	0.259	0.002
RS 1 year	0.156	0.05

HT, heart transplantation; MPI, myocardial performance index; CsA, cyclosporin A; MethPD, methylprednisolone; RS, rejection score.

inadequate measures of the CsA absorption [14]. This may also explain the discrepancy between our data and the study of Valentine *et al.* [15] that failed to show a direct relation between impaired diastolic function and CsA use. Another finding of the present study, in particular the direct relation between MPI and cumulative MethPD dosage, has not been previously shown and provides further evidence for a link between impaired ventricular function and higher number of treated rejection episodes.

The progressive increase of MPI with time from HT is likely to indicate the well-known progressive deterioration of cardiac allograft dysfunction in the long term, regardless of angiographically documented CAV [1].

Another finding of the present study, in particular the inverse relation between graft dysfunction, as assessed by an abnormal MPI, and age at HT, not previously shown [15,16], is in accordance with an immune-mediated basis for graft dysfunction; indeed younger recipient age has been identified as a risk factor for acute and CAV [1,17]. So far, the link between AR and systolic and/or diastolic allograft dysfunction has remained elusive. Some studies suggested an association between AR and allograft diastolic dysfunction in long-term HT recipients [15,16]. Valantine *et al.* found that HT recipients with restrictive-constrictive physiology had significantly more previous rejection episodes compared with the nonrestrictive group [15]. In accordance, Aziz *et al.* documented an association between impaired LV diastolic dysfunction and rejection incidence [16]. However, none of these studies found a direct significant relation of systolic graft dysfunction and AR. Study limitations included low patients [15], short follow up [16], and lack of quantification of the individual rejection burden in terms of RS [15,16]. Our findings give evidence for the prognostic value of AR burden on LV function in long-term cardiac allograft recipients.

A limitation of the present study, on stable long-term HT patients, is that no endomyocardial biopsies were

taken, because there was no clinical suspicion of AR and in all patients LVEF was preserved by echocardiography. However, the possibility that our findings on MPI are related to undetected AR seems unlikely. In fact, initially AR frequency is low after the first year, and in none of our 154 patients AR was suspected or diagnosed in the following months. Secondly, some [18] but not all studies [19,20] found that MPI is abnormal during AR.

In conclusion, this study is the first to highlight the potential role of MPI in the assessment of early LV dysfunction in long-term cardiac allograft recipients with preserved LVEF. Our correlative data suggest an immune-mediated basis for chronic LV dysfunction. MPI was easily to obtain in all patients and may thus be of adjunctive use in patients with poor image quality and nondiagnostic 2D and Doppler-echo findings. However, our findings in stable long-term HT patients should not be extrapolated to patients in the first 6–12 months, as AR might cause reversible MPI changes, which resolve with treatment. Further, prospective studies are warranted to assess the potential role of abnormal MPI as a negative prognostic marker in HT.

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