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HAL Authorization

1 **High-sensitive Troponin T – a novel biomarker for prognosis and disease**
2 **severity in patients with pulmonary hypertension**

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23 ***Key words***

24 biomarkers, pulmonary hypertension, high sensitive Troponin T, prognosis, six-minute
25 walk test, echocardiography

1 **Abstract**

2 **Background.** Pulmonary hypertension is the leading cause of fatal right ventricular failure.
3 However rarely detectable, conventional troponin T (cTnT) is a significant prognostic
4 marker.

5 Therefore, this study evaluates the usefulness of a novel high-sensitive troponin T (hsTnT)
6 assay as a parameter for functional and prognostic evaluation of PH patients.

7 **Methods.** In 55 pulmonary hypertension patients (idiopathic n=20, chronic
8 thromboembolic n=30, and interstitial lung disease n=5) with a mean pulmonary artery
9 pressure 45 ± 18 mmHg, troponin T was measured by 4th generation conventional assay and
10 a novel high-sensitive assay with a lower detection limit at 2 pg/mL (total imprecision
11 $< 10\%$ at 99th percentile value (13.4 pg/mL)).

12 **Results.** In 90.9% of patients, troponin T was detectable using the hsTnT assay and in
13 30.9% using the 4th generation assay. Concentrations $> 99^{\text{th}}$ percentile were seen in 27.3%
14 using hsTnT as compared to 10.9% using 4th generation assay. Five of 6 patients with
15 values > 30 pg/ml (4th generation assay), or > 29.5 pg/mL (hsTnT assay) died during 12-
16 month follow-up. There was a correlation between hsTnT and six minute walk distance ($r =$
17 0.92 , $p = 0.0014$), right ventricular systolic strain ($r = 0.95$, $p = 0.0018$) and strain rate ($r = 0.82$,
18 $p = 0.0021$). In AUC analysis, hsTnT predicted death at least as effective as heart-type fatty
19 acid binding protein (hFABP) or NT-pro BNP. Moreover, hsTnT predicted WHO class > 2
20 better than NT-proBNP or hFABP.

21 **Conclusions.** In pulmonary hypertension patients, the novel biomarker high-sensitive
22 troponin T is associated with death and advanced WHO class, and related to systolic right
23 ventricular dysfunction and impaired six minute walk distance.

1 ***Introduction***

2 Chronic pulmonary hypertension (PH), a potential consequence of many distinct disease
3 mechanisms, is characterized by progressive dyspnea and limitation in exercise capacity
4 [1]. While the clinical symptoms in PH may result from peripheral airway dysfunction,
5 skeletal muscle weakness and progressive right ventricular (RV) failure, RV dysfunction is
6 the most important determinant of patients' outcome [2, 3]. In the recent years substantial
7 progress has been achieved in the treatment of PH, mostly due to improved
8 pharmacotherapy [4]. However treatment is not only expensive but also associated with
9 severe side-effects in a relevant proportion of patients. Therefore non-invasive
10 identification of high risk subgroups may improve not only risk assessment but also
11 guidance for selection of treatment modalities and intensity.

12 Multiple clinical indexes have been applied to better assess severity of disease and risk in
13 PH patients. WHO functional class, 6 minutes walking distance (6MWD), anatomic and
14 functional echocardiographic parameters, cardiac biomarkers and exercise testing by stress
15 echocardiography or cardio-pulmonary exercise testing are the most commonly used
16 surrogates [5-8].

17 Since RV dysfunction is the major predictor of adverse outcome much attention has been
18 directed to improve the assessment of the RV contractile function and reserve [9]. Strain
19 analyses by tissue Doppler have become the standard measures to study contractile function
20 of left ventricular myocardium. Recent findings indicate that strain and strain rate are also
21 useful to assess RV function and may serve – in conjunction with N-terminal pro brain
22 natriuretic peptide (NT-proBNP) – as surrogates of contractile function of the overloaded
23 RV [10].

24 Cardiac troponins (cTn) constitute the preferred markers for diagnosis of myocardial
25 infarction and for identification of myocardial damage. While elevated cTn have been
26 found useful to predict adverse hemodynamics and prognosis after acute pulmonary
27 embolism their role is still controversial in patients with chronic pulmonary embolism
28 potentially due to the low prevalence of elevated cTn using less sensitive assay generations.

29 In patients with PH, increased serum levels of cTn have been found to correlate with higher
30 heart rates, lower mixed oxygen saturation, pronounced exercise limitation and blood levels
31 of B-type natriuretic peptides [8]. Conversely, measurement of heart-type fatty acid-binding
32 protein (hFABP) was found more useful for risk assessment in patients with chronic

1 thromboembolic pulmonary hypertension although cTnT remained an ominous prognostic
2 sign when detectable [11].

3 Recently, modifications of cTnT assays have been introduced that result in higher
4 analytical sensitivity and the ability to measure concentrations at the 99th percentile of a
5 reference population with an imprecision of less than 10 %.

6 The primary aim of the study was therefore to evaluate the usefulness of a novel high-
7 sensitive troponin T assay (hsTnT) as a parameter for clinical and functional evaluation,
8 and for prognostic stratification of PH patients in contrast to the established biomarkers.

9

10 ***Materials and Methods***

11 This prospective study enrolled 55 consecutive patients with PH. The diagnosis was
12 established by right heart catheterization, pulmonary angiography, spiral computer
13 tomography, and echocardiography. Significant coronary artery disease was excluded by
14 stress testing or coronary angiography.

15 Patients were treated according to current guidelines for PH treatment [12]. They were
16 studied while on stable doses of their medications over the last four weeks and showed no
17 clinical or radiological signs of cardiopulmonary decompensation.

18 Given the interference between kidney function and biomarker concentrations patients with
19 severe renal failure (creatinine clearance < 60 mL/min/1.73m²) were excluded.

20 The protocol was approved by the local ethics committee of the University of Heidelberg,
21 and all patients gave written informed consent prior to inclusion.

22

23 **Assessment of cardio-pulmonary function**

24 The six minute walk test (6-MWT) [13] and two-dimensional transthoracic
25 echocardiography was performed using standard protocols [14].

26 Two-dimensional transthoracic echocardiography for non-invasive imaging was used to
27 obtain information on right ventricular (RV) and left ventricular (LV) function including
28 assessment of RV end-diastolic area, RV end-systolic area, RV fractional area change, RV
29 to LV end-diastolic area ratio, and LV ejection fraction left ventricle (LV) by RV end-
30 diastolic area, RV end-systolic area, RV fractional area change, RV to LV end-diastolic
31 area ratio, LV ejection fraction [14]. Moreover, systolic pulmonary arterial pressure (sPAP)
32 and the Tei-Index (RV myocardial performance index) were measured as described
33 previously [15]. For RV systolic functional assessment, the tricuspid annular systolic

1 excursion (TAPSE) was measured from the apical 4-chamber view as recommended earlier
2 [16].

3 Systolic strain and strain rate were derived from tissue Doppler velocities [17]. A strain
4 region of interest was placed in the basal segment of the RV free wall. Measurements of 3
5 to 5 heart cycles were recorded and averaged for all analyses.

6

7 **Blood Sampling for Biomarker Analysis**

8 Blood samples were drawn from a peripheral vein and analyzed for serum NT-proBNP,
9 hFABP, high-sensitivity (hs) TnT and cTnT.

10 HsTnT was measured using the latest pre-commercial version of the hsTnT assay (Roche
11 Diagnostics, Mannheim, Germany). The lower detection limit of this assay was 2 pg/mL
12 (=0.002 μ g/L). Improvement of sensitivity and precision was achieved by increasing the
13 sample volume to 50 μ L, optimizing the degree of ruthenylation of the signal antibody, and
14 optimizing the buffer composition to reduce background signal. As described previously,
15 the inter-assay coefficient of variation was 8% at 10pg/mL and 2.5% at 100pg/mL. The
16 intra-assay coefficient of variation was 5% at 10pg/mL and 1% at 100pg/mL [18]. Normal
17 reference values were established from three reference studies including 1934 apparently
18 healthy volunteers and blood donors between 20 and 71 years. The 99th percentile value
19 was determined at 13.4 pg/mL.

20 CTnT was measured using the 4th generation commercial one-step EIA based on
21 electrochemiluminescence technology (Roche Diagnostics, Mannheim, Germany). The
22 lower detection limit is 0.01 μ g/L with a recommended diagnostic threshold of 30 pg/mL
23 (corresponding to 0.03 μ g/L) [18].

24 NT-proBNP was measured using a highly sensitive and specific electrochemiluminescence
25 immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany). The inter-assay
26 coefficient of variation (CV) has is 3.2 – 2.4% from 175 – 4962 pg/mL and 5.7% at 64
27 pg/mL. The measurement range extends from 5 to 35,000 pg/mL.

28 HFABP was measured with the turbidimetric latex immunoassay as described previously
29 [19]. The intra-assay coefficient of variation was 5.3 % at 7.7 μ g/L (= 7700pg/mL) and 1.2
30 % at 41.6 μ g/L (= 4160 pg/mL). The inter-assay coefficient of variation was 9.3 % at 7.3
31 μ g/L (= 7300pg/mL) and 2.7 % at 41.4 μ g/L (= 4140pg/mL). The minimal detection limit
32 of the assay was 1.1 μ g/L (= 1100 pg/mL).

33

1 **Data analysis**

2 All results are expressed as mean \pm SD, or as medians with 25th and 75th quartiles.
3 Correlations between biomarkers and functional test results were calculated using Pearson
4 product-moment correlation coefficient. Levels of biomarkers were log-transformed before
5 analysis as needed to stabilize the variance. We used ANOVA to test the difference
6 between biomarker levels in WHO functional classes using Student-Newman-Keuls test for
7 all pair wise comparisons. A two tailed p-value of 0.05 was regarded significant. Statistical
8 analysis was performed using Medcalc (MedCalc Software, Version 10.3.2, Mariakerke,
9 Belgium).

13 **Results**

14 A total of 55 patients were included with a diagnosis of PH which was idiopathic in 20
15 cases, thromboembolic in 30 cases, and associated with interstitial lung disease in 5 cases.
16 Among the 55 patients, 21 patients (38%) were in WHO functional class 3 and 4, and 20
17 patients had a 6MWD of less than 150m indicating severe right heart failure. Consistently,
18 NTproBNP levels were elevated above 125 pg/mL in 48 PAH patients (87%). The baseline
19 characteristics of the entire cohort are given in Table 1.

20 There was a close relationship between WHO functional class and biomarker results,
21 6MWT and echocardiographic parameters. As WHO functional class increased there was a
22 significant rise in biomarker concentrations and a consistent decrease of 6MWT, strain and
23 strain rate in echocardiography.

24 The prevalence of patients with positive cTnT results varied widely and was closely related
25 to the cTnT assay and the cutoff used. Accordingly, cTnT was detectable in 50 of 55
26 patients (90.9 %) using the hsTnT assay whereas only 17 patients (30.9 %) had
27 concentrations above the lower detection limit (10 pg/mL) using the 4th generation cTnT
28 assay. Using the 10 % CV as the decision cutoff, cTnT was positive in 6 patients (10.9 %)
29 whereas 15 patients (27.3 %) had values exceeding the 99th percentile value using the
30 hsTnT assay.

31 Within 12 months after enrollment, a total of 5 patients died due to progressive right
32 ventricular failure without the indication of acute pulmonary embolism. All of these
33 patients were in WHO class IV and disclosed cTnT values above 30 pg/ml. Conversely, no

1 patient died with hsTnT $< 0.013\mu\text{g/ml}$, which is the 10 % CV and 99th percentile value
2 ($p < 0.0001$), respectively.

3 Regarding the ability to predict death within 12 months, cTnT $> 30 \text{ pg/ml}$ predicted all
4 deaths (Table 2) whereas NT-pro BNP and hFABP were less predictive. HsTnT was also
5 superior in its relationship with functional capacity (WHO class), as compared to cTnT,
6 NT-proBNP and hFABP (Table 3). HsTnT levels were significantly higher in patients with
7 WHO functional class 3 and 4 as compared to patients with mild exercise limitation (Figure
8 1).

9 There was a significant correlation between hsTnT levels and exercise capacity as assessed
10 by the 6-MWD (Figure 2). Notably, the hsTnT was more closely related to 6-MWD than
11 NT-proBNP was (Figure 3).

12 Moreover, the echocardiographic indices of RV contractile function systolic strain and
13 strain rate showed a significant correlation to hsTnT (Figure 4 A and B). In contrast, there
14 was no significant relationship between the Tei-Index reflecting diastolic function (data not
15 shown).

16 While cTnT is regarded as indicator of myocardial injury, NT-proBNP often reflects
17 myocardial overload. The relation between hsTnT and NT-proBNP levels is shown in
18 Figure 5.

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22 **Discussion**

23 The major findings of the present study are:

24 First, the use of a high-sensitive cTnT assay enables detection of cTnT in more than 90% of
25 all patients with PH as compared to 30.9% using the currently used 4th generation assay of
26 the same manufacturer. Concentrations above the 99th percentile of a healthy reference
27 population are encountered in 27.3% of cases with the new hsTnT assay but only in 10.9%
28 of cases using the 4th generation assay when using the cutoff with an imprecision of less
29 than 10% CV. This improved detection is achieved by higher analytical sensitivity with a
30 lower limit of detection at 2 pg/ml as compared to 10 pg/ml with the currently used 4th
31 generation cTnT assay as well by an improved assay precision at the 99th percentile of a
32 healthy reference population.

1 Second, a cTnT value above 30 pg/mL as measured by the 4th generation cTnT and hsTnT
2 are excellent predictors of death within 12 months and perform at least as good as hFABP
3 or NT-proBNP.

4 Third, cTnT concentrations rose with increasing severity of functional WHO class and
5 there was a clear inverse correlation between detectable cTnT concentrations and
6 echocardiographic parameters of systolic RV dysfunction as well as reduced exercise
7 capacity as measured by the 6MWD. Serum levels of hsTnT proved superior to cTnT,
8 hFABP and NT-pro BNP to identify patients with more severe PH in WHO functional class
9 > 2.

10 Previous studies have demonstrated that detectable cTnT levels in patients with acute
11 pulmonary embolism (PE) are associated with unfavorable prognosis [20-22].

12 In patients with confirmed PE the prevalence of cTnT or cTnI above the 99th percentile or
13 the 10 % CV has been reported as high as 32 and 21%, respectively [20].

14 In contrast to acute PE, the prevalence of elevated cTn concentrations in PH is much lower.

15 Torbicki et al. first reported on the potential prognostic role of detectable cTnT in PH [8].

16 Although the prevalence of detectable cTnT was only 14 %, elevated levels appeared to be
17 associated with a poor prognosis. In contrast to acute PE, this low prevalence of elevated
18 cTn together with the finding that cTn elevations were exclusively found in patients with
19 advanced stages of PH raised the contention that cTn may not be useful in PH. Therefore,
20 several other biomarkers including heart-type fatty-acid binding protein, brain-type
21 natriuretic peptides were tested in a few small cohorts [8, 22-26] and in a single prospective
22 trial [11]. Lankeit et al. reported on the largest cohort that included 93 patients with chronic
23 thromboembolic pulmonary hypertension. In this study, hFABP concentrations were
24 significantly higher in those patients with an adverse outcome. Disappointingly, cTnT was
25 not helpful due to a very low prevalence of only 4 % of patients with levels above the lower
26 detection limit (>0.01 µg/L). However, all patients with detectable cTnT concentrations
27 died rendering cTnT an ominous indicator of outcome when present [11].

28 More recently, more refined generations of cTn assays with higher analytical sensitivity,
29 i.e. lower detection limit and adequate precision to measure low troponin concentrations at
30 the 99th percentile of a healthy reference population, became available and have stimulated
31 the hypothesis that the use of such a high-sensitive cTn assay may improve risk
32 stratification and may allow insights into disease pathophysiology. In the present study, the
33 use of hsTnT enabled identification of more patients with a cTnT concentration above the
34 99th percentile. The cTnT concentrations were detectable in all patients and only 27.3 % of

1 all patients had cTnT concentrations above the 99th percentile value. With the present study,
2 elevated cTnT values are no longer restricted to WHO class 4 but can also be found in less
3 advanced WHO functional classes. The present study found that hsTnT performed at least
4 comparable to hFABP or NT-pro BNP for prediction of death within 12 months. Moreover,
5 hsTnT performed significantly better regarding prediction of more advanced WHO
6 functional class than cTnT, hFABP, and NT-pro BNP. Although the number of patients and
7 events was low, we could clearly demonstrate the adverse prognosis associated with
8 elevated cTnT concentrations above the 99th percentile.

9 The underlying pathomechanisms for a rise in cTn after acute PE or in patients with chronic
10 PH remain unclear. Several mechanisms have been proposed, including myocardial
11 ischemia and necrosis from acute increase in RV afterload, or myocardial stress from
12 increased wall tension. In pulmonary embolism, elevated cTn levels are associated with the
13 presence of RV dysfunction [20, 22].

14 In patients with chronic left heart failure, elevated cTn levels have been observed in
15 correlation with functional impairment and unfavorable prognosis [27-29]. This is in
16 concert with the present findings in PH with chronic RV dysfunction. In the present study,
17 there was a correlation between echocardiographic parameters of RV function and elevated
18 cTn.

19 In the hsTnT positive patients revealed significant RV dysfunction and reduced regional
20 contractility during echocardiography. Consistently, RV strain and strain rate were
21 inversely related with hsTnT values indicating, that hsTnT is an indicator of systolic RV
22 dysfunction. In contrast, no association was found between diastolic RV dysfunction as
23 measured by the Tei-index and troponin level. These findings are particularly important,
24 since previous observations have promoted echocardiography as a tool for the functional
25 evaluation of patients with PH [10, 30]. In this context, strain echocardiography has been
26 reported as surrogate of pulmonary hemodynamics in smaller heterogeneous populations
27 including patients with PH due to ischemic left ventricular failure, or chronic
28 thromboembolism [31].

30 **Study limitations**

31 The present study has limitations: On the one hand, the small sample size and the low
32 number of fatal events in the present investigation might have attenuated the statistical and
33 clinical performance of the biomarkers tested. Especially, a larger number of fatal events
34 and a longer observational period in a future study will substantiate the role of hsTnT as a

1 novel marker of prognosis. Therefore, the present observations will prompt the validation
2 of the novel biomarker hsTnT in a larger multi-center PH cohort by us and others.

3 On the other hand, hsTnT and NT-proBNP were measured from a single frozen blood
4 sample obtained on presentation. Notably, cTnT was measured serially after 6 hours and
5 usually on the day following admission as a typical rise/fall of cardiac troponin is required
6 for the diagnosis of acute myocardial infarction and in order to distinguish an acute from a
7 chronic troponin elevation. While troponin concentrations above the 99th percentile value
8 may also be associated with stable coronary heart disease, acute or chronic left ventricular
9 heart failure, myocarditis, drug toxicity and other cardiac diseases, an elevation of cTn is
10 almost always associated with an unfavorable prognosis [27-29, 32]. The measurement of
11 biomarker levels in only a single blood sample for functional and prognostic evaluation of
12 PH patients seems to comply with the recommended monitoring during visits in a
13 specialized out-patient clinic [33].

14 **Conclusion**

15 This pilot study on 55 well characterized patients with PH indicates the usefulness of cTnT
16 as biomarker of disease severity when measured with the high sensitive assay. It is
17 tempting to speculate from other observations studying patients with acute increase of RV
18 afterload due to acute PE, that a combination of biomarker levels and echocardiography
19 parameter of RV function will improve risk stratification by increasing the positive
20 predictive value of either test. In order to test this hypothesis larger studies are needed to
21 test the predictive power of hsTnT and its contribution to therapeutic decisions.
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5 Society of Cardiology (ESC) and the European Respiratory Society (ERS). (2009)
6 European Heart Journal 30, 2493–2537
7

1 **Legends**

2

3 Table 1

4 Baseline Characteristics of the Study Population.

5

6 Table 2

7 Prediction of death within 12 months using cardiac Troponin T (cTnT), high sensitive
8 troponin T (hsTnT) > 29.05 pg/mL, heart-type fatty acid binding protein (hFABP), or N-
9 terminal pro B-type natriuretic peptide (NT-proBNP).

10

11 Table 3

12 Prediction of WHO functional class > 2 using cTnT, hsTnT, hFABP and NT-proBNP.

13

14 Figure 1

15 High sensitivity troponin T levels in 55 patients with pulmonary hypertension assigned to
16 the WHO functional classification.

17

18 Figure 2

19 Correlation between high sensitivity troponin T and 6- minute walk distance in 55 patients
20 with pulmonary hypertension.

21

22 Figure 3

23 Correlation between N-type pro brain natriuretic peptide and 6-minute walk distance in 55
24 patients with pulmonary hypertension.

25

26 Figure 4

27 Correlation between high-sensitivity troponin T and right ventricular systolic strain during
28 echocardiography.

29

30 Figure 5

31 Correlation between high-sensitivity troponin T and right ventricular systolic strain rate
32 during echocardiography.

33

34

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1
2 **Table 1**

	Patients with Pulmonary Hypertension (n=55)
Age, years	53.6±12.4
male / female	22 / 33
WHO functional class 2/ 3 / 4	34 / 15 / 6
6-min walk test, m	201 ± 100
NT-proBNP, pg /mL	1535 ± 946
PAPm, mmHg	45 ± 18
PCWP, mmHg	9.5 ± 4.3
LV cardiac output, L/min	3.3 ± 1.8
PVR, Wood units	6.9 ± 3.5
sPAP, mmHg (Echo)	84.5 ± 22.8
Tei-Index	0.58 ± 0.14
TAPSE, mm	6.3 ± 2.4
RV end-diastolic area, cm ²	24.1 ± 6.0
RV end-systolic area, cm ²	17.9 ± 7.0
RV fractional area change, %	24.7 ± 10.6
RV to LV end-diastolic area ratio	1.4 ± 0.5
LV ejection fraction, %	73 ± 5
Strain, %	-14.2 ± 4.6
Strain rate, s ⁻¹	-0.26 ± 0.14

3
4 Data are presented as mean ± SD. LV = left ventricle, NT-proBNP = N-terminal pro B-type
5 natriuretic peptide, PAPm = mean pulmonary artery pressure, sPAP = systolic pulmonary
6 artery pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular
7 resistance, RV = right ventricle, TAPSE = tricuspid annular plane systolic excursion.

8

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1 **Table 2**

2

	cTnT	hsTnT	hFABP	NT-proBNP
Sensitivity %	100	100	80	100
Specificity %	100	100	82	82
NPV	100	100	97.5	100
PPV	100	100	26.7	33.4

3

4 NPV: negative predictive value; PPV: positive predictive value

5

6

7

8

9 **Table 3**

	cTnT	hsTnT	hFABP	NT-proBNP
Sensitivity %	81	100	71.4	100
Specificity %	100	100	82.4	97.1
NPV	90.2	100	82.9	100
PPV	100	100	66.5	95.1

10

11 NPV: negative predictive value; PPV: positive predictive value

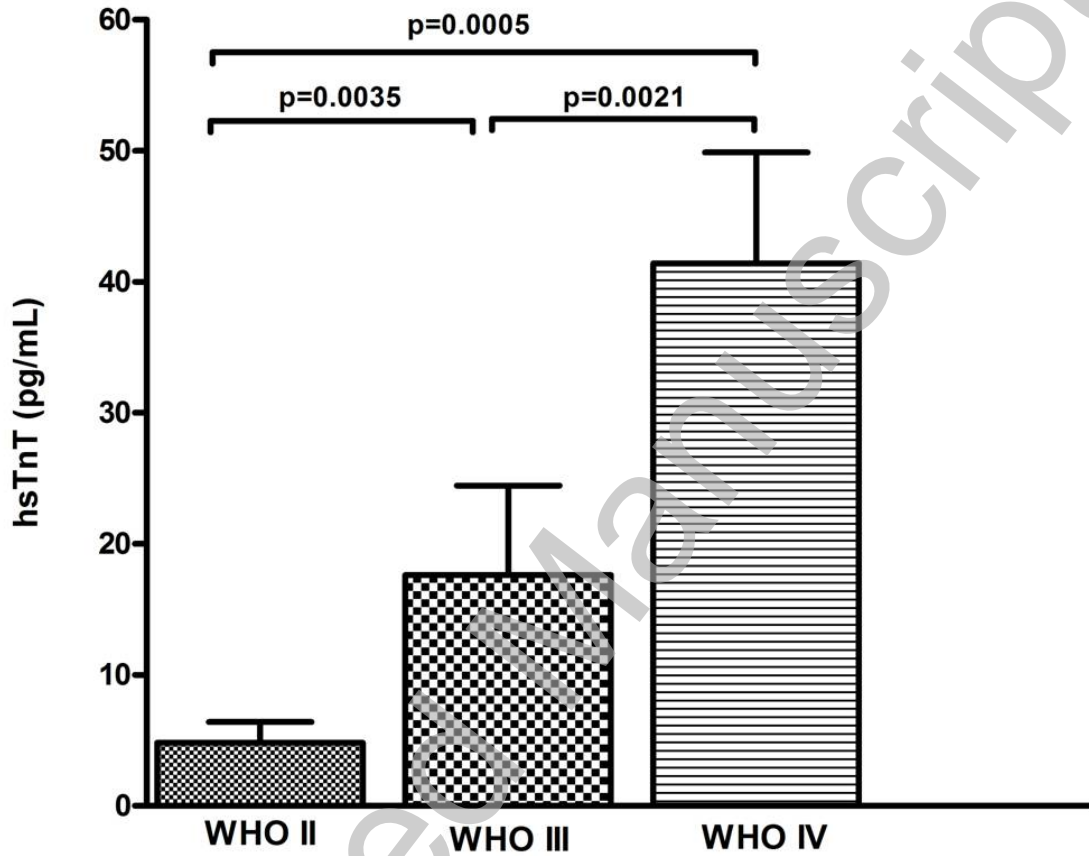
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1

2 **Figure 1**

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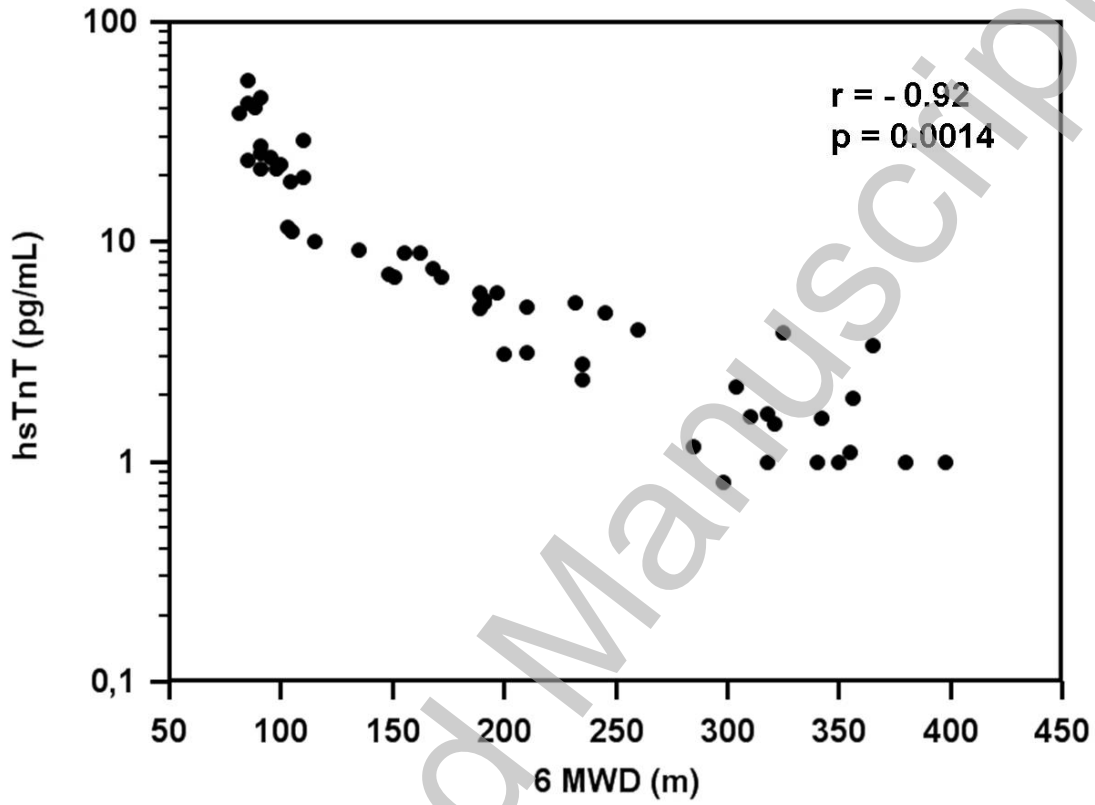
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2 **Figure 2**

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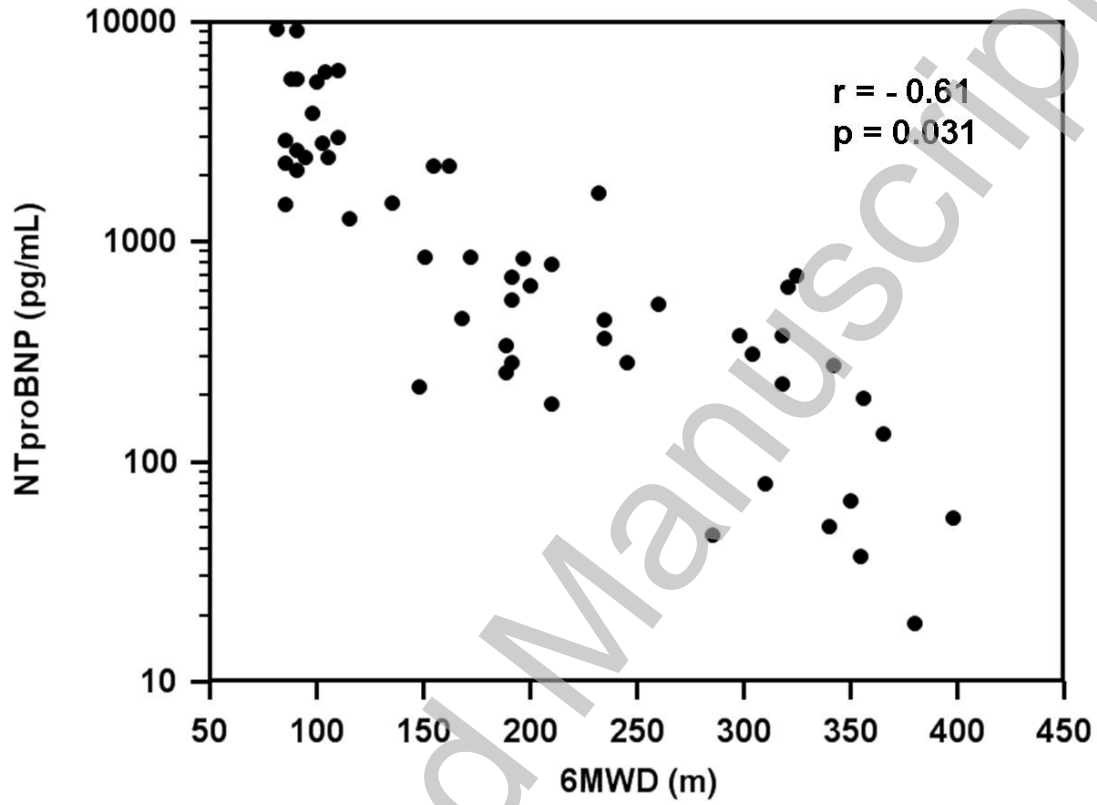
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2 **Figure 3**

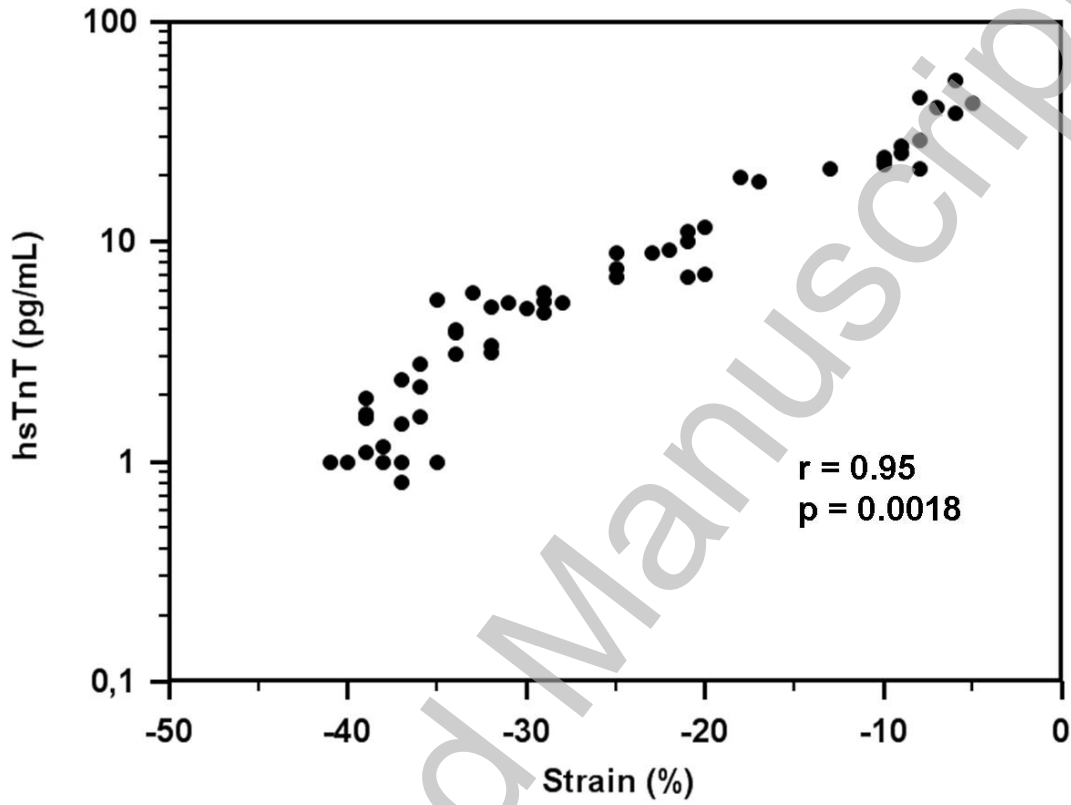
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1

2 **Figure 4 A**

3



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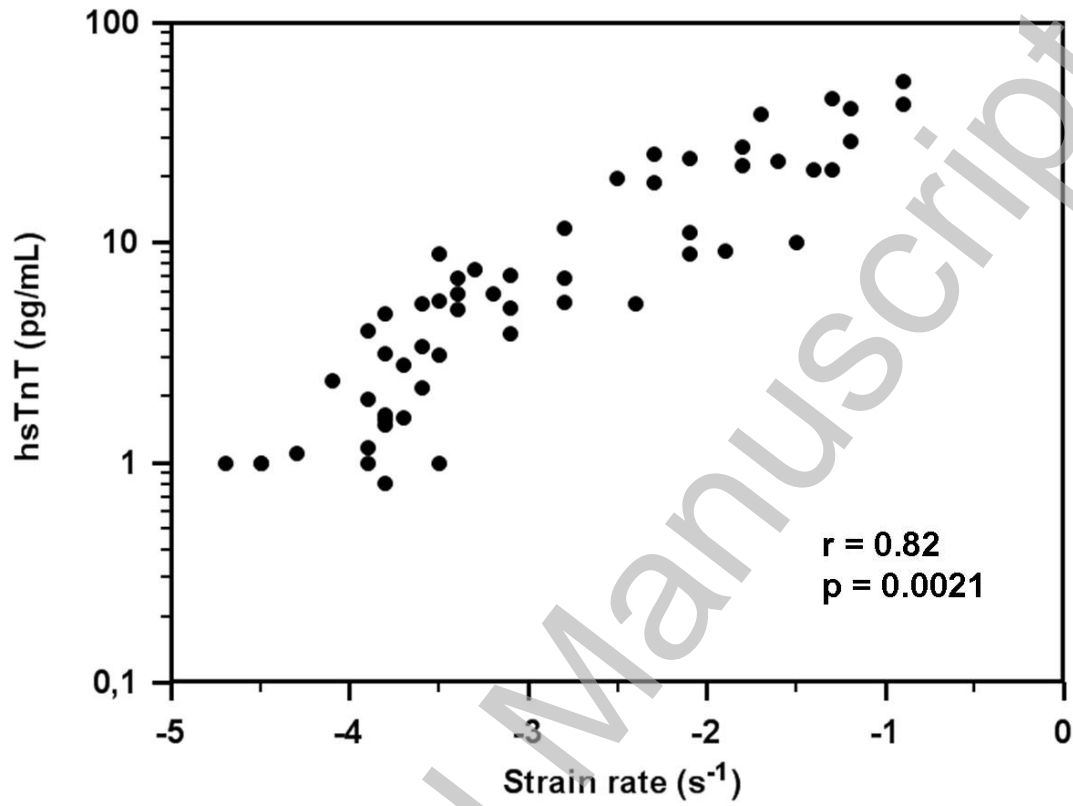
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1 **Figure 4 B**

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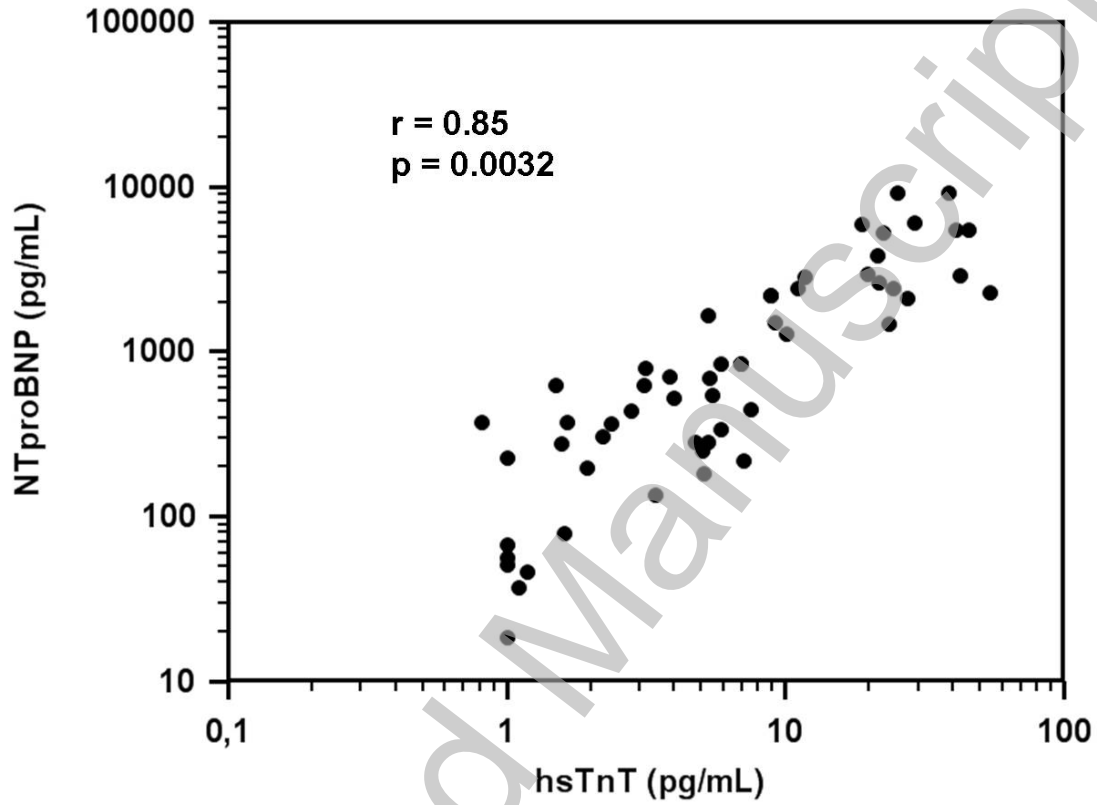
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2 **Figure 5**

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