Objective: To determine the prevalence of pulmonary arterial hypertension in asymptomatic patients with 2 types of extensive slow-flow vascular malformations: extensive venous malformations or Klippel-Trénaunay syndrome (KTS).

Design: Case-control.

Setting: Multidisciplinary center for vascular anomalies.

Patients: A consecutive sample of 32 patients with slow-flow vascular malformations of at least 15% of the body surface was identified retrospectively and matched by age and sex with 32 healthy controls.

Interventions: Standard 2-dimensional transthoracic Doppler echocardiography. Venous samples were obtained the same day that echocardiography was performed.

Main Outcome Measures: Pulmonary artery systolic pressure (PASP) was determined. Levels of D-dimer, fibrinogen, and von Willebrand factor (vWF) in plasma were measured.

Results: Patients had a mean (SD) PASP that was significantly higher than that of healthy controls (42.16 [8.49] mm Hg in patients vs 27.69 [6.54] mm Hg in healthy controls; \(P < .001\)). No significant differences in PASP were found between patients with KTS and patients with venous malformations (\(P = .80\)). We observed significant differences in the mean (SD) levels of vWF between patients and healthy controls (124.41% [52.28%] in patients vs 92.69% [28.92%] in controls; \(P = .01\)) and also in levels of D-dimer (1032.99 [1367.0] ng/mL in patients vs 102.97 [29.39] ng/mL in healthy controls; \(P < .001\)). There was a moderate positive correlation between levels of vWF and levels of PASP (\(r = 0.42; \ P = .001\)) and a high positive correlation between D-dimer and PASP (\(r = 0.52; \ P < .001\)).

Conclusions: The presence of pulmonary arterial hypertension in patients with extensive slow-flow vascular malformations is not an isolated feature but is relatively frequent. Levels of D-dimer correlate with PASP in these patients.

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Low-flow vascular malformations are divided into venous, lymphatic, and combined malformations such as Klippel-Trénaunay syndrome (KTS). Venous malformations are ectatic vessels that are morphologically and histologically similar to veins but deficient in smooth muscle. Klippel-Trénaunay syndrome is characterized by venous, lymphatic, and capillary malformations (port-wine stain); skeletal hypertrophy; and increased soft tissue in 1 or more limbs. Coagulation disorders, which have been reported in patients with venous malformations and KTS, can produce hemorrhage and thrombosis. The magnitude of the coagulopathy correlates with the severity of the malformation and is a localized intravascular coagulation (LIC), which differs from the diffuse intravascular coagulation of Kasabach-Merritt syndrome. LIC consists of a local consumption of coagulation factors inside the malformation due to venous stasis, resulting in the formation of multiple phleboliths. Elevated D-dimer levels are highly specific for venous malformations (or the venous component in combined malformations). The main complication of KTS is thrombophlebitis, which occurs in 20% to 45% of patients and leads to pulmonary embolism in 4% to 25% of cases. Thromboembolic events can cause chronic thromboembolic pulmonary hypertension (CTEPH), which has also been described as a complication of pure venous malformations, probably due to thromboembolic events. CTEPH is a type of pulmonary arterial hypertension (PAH). There are some reports of PAH in patients with vascular malformations who had symp-
toms such as dyspnea. This study examines the prevalence of PAH in asymptomatic patients with slow-flow vascular malformations.

**METHODS**

Sample patients had extensive slow-flow vascular malformations (venous or combined malformations such as KTS) and did not have cardiovascular risk factors, including variables that could be related to PAH, or a history of symptomatic pulmonary embolism. All patients were asymptomatic, without any signs or symptoms of heart failure. A vascular malformation was considered to be extensive if it involved at least 15% of the patient's body surface area (equivalent to ≥1 complete lower extremity) (Figure 1). All venous lesions had infiltrated the muscular plane and involved the skin and subcutaneous cell tissue. A patient was diagnosed as having KTS when soft-tissue and/or bony hypertrophy, port-wine stain, and venous varicosities were all present. The exclusion criteria were small or intermediate slow-flow malformations, high-flow malformations, or the presence of cardiovascular disease.

The diagnosis was made by clinical examination and confirmed by Doppler ultrasonography when necessary. Thirty-two healthy controls, relatives and friends of the authors, with no vascular disorder of any kind and without cardiovascular risk factors, were also included. They were matched by age and sex with the patients, and they were tested in the same period as the patients. The study was approved by the ethics committee of the University Clinic of Navarra (Pamplona, Spain), and written informed consent was obtained from all participants.

**PROCEDURES**

Patients underwent a standard 12-lead electrocardiogram (ECG) and transthoracic Doppler echocardiography (TTDE). The sensitivity of TTDE to establish the presence of PAH is 79% to 100%, and the specificity is 60% to 98%. Pulmonary arterial systolic pressure (PASP) (determined by the velocity of tricuspid regurgitation by continuous wave Doppler in the echocardiogram) was measured. We considered PASP values of 50 mm Hg or higher to be pathological. Values of 37 to 50 mm Hg were considered borderline, and values equal to or lower than 36 mm Hg were considered normal.

Venous samples were drawn from the cubital vein the same day as the echocardiography study. Plasma was removed and stored at −80°C until analysis. To determine vWF levels, we used STA LIATEST vWF reagent (Diagnostica Stago/Roche, Asnières, France) and the STA Compact analyzer (Stago/Roche). To determine levels of fibrinogen, we used Multifibren U (Siemens Healthcare diagnostics products, Marburg, Germany) and the BCS XP Siemens system. We measured the levels of D-dimer, using D-dimer PLUS (Dade Behring Marburg GmbH, Marburg, Germany) and the BCS XP Siemens system.

**STATISTICAL ANALYSIS**

All results were analyzed using SPSS statistical software (version 15.0; SPSS Inc, Chicago, Illinois). In all cases, we considered 2-sided P < .05 to be statistically significant. Continuous variables were compared using t test or with Mann-Whitney test (when nonparametric tests were necessary). Correlations between continuous variables were examined using Spearman rank correlation. To determine if there were differences in D-dimer values among groups of patients with normal, borderline, and pathological PASP, we used the Kruskal-Wallis test and then made post hoc paired comparisons using Bonferroni-corrected Mann-Whitney tests.

**RESULTS**

**SAMPLE CHARACTERISTICS**

Sixty-three consecutive patients with slow-flow vascular malformations referred to our multidisciplinary center for evaluation were included. The study sample was compared with 32 controls. The population was 63 patients with slow-flow vascular malformations, 43 venous malformations (VM), 18 Klippel-Trenaunay syndrome (KTS), and 2 lymphatic malformations (LM). The patients were divided into two groups: (1) Patients assessed for eligibility for the echocardiography study: 63 patients (VM, 43; KTS, 18; LM, 2) and (2) Patients analyzed for blood levels of vWF, fibrinogen, and D-dimer: 32 patients (VM, 14; KTS, 18).

**Figure 1.** Two patients. A, A 6-year-old patient with extensive venous malformation involving right buttock and lower limb. B, A 26-year-old man with Klippel-Trenaunay syndrome with port-wine stain of geographic morphology and dark red-purple color, and extensive venous malformation (several phlebectasias in the thigh and leg).

**Figure 2.** Flowchart. KTS indicates Klippel-Trenaunay syndrome; LM, lymphatic malformation; VM, venous malformation; WF, von Willebrand factor.
vascular anomalies in Pamplona were evaluated from 2008 through 2009. Twenty-nine patients with venous malformations and 2 with lymphatic malformations were excluded because they did not meet the criteria regarding the extent of the lesions (Figure 2). All patients with KTS were also included. A total of 32 patients (15 women and 17 men; mean age, 27 years [range, 3-62 years]) fulfilling the criteria of extensive slow-flow malformations were included in this retrospective analysis. Eighteen patients had KTS, and 14 had extensive venous malformations. Clinical characteristics of subjects and controls are compared (Table 1), and patients with venous malformations and KTS are described herein (Table 2).

**CARDIOLOGIC FINDINGS**

Findings from all ECGs were normal except for 1 patient with KTS who presented with left bundle branch block. In the echocardiogram, 7 patients (22%) showed PASP values of 50 mm Hg or higher (pathological), 16 (50%) showed values of 37 to 50 mm Hg (borderline), and 9 (28%) had PASP equal to or lower than 36 mm Hg (normal). None of the healthy controls showed PASP values of 50 mm Hg or higher, 2 (6%) had values of 37 and 50 mm Hg (borderline), and 30 (94%) had PASP equal to or lower than 36 mm Hg (normal).

Patients had a mean (SD) pulmonary pressure that was significantly higher than that of healthy controls (42.16 [8.49] mm Hg in patients vs 27.69 [6.54] mm Hg in controls; \( P < .001 \) (Figure 3). There were no differences in other echocardiographic measures. No differences were found in the mean PASP values between the KTS and venous malformation groups (42.50 [8.67] mm Hg in patients with KTS vs 41.71 [8.54] mm Hg in patients with venous malformations; \( P = .80 \)).

There were 2 patients diagnosed as having KTS with hemicorporeal affection and another with involvement of both lower extremities. When we compared the PASP values of these 3 patients with those of the rest of the patients, we observed statistically significant differences (the mean [SD] PASP values in patients with very extensive malformations were 52.67 [8.08] vs 41.07 [7.87] in the rest of the patients; \( P = .02 \)).

All children younger than 15 years with KTS (n=4) and 4 of the 5 children with venous malformations had borderline or pathologic PASP. D-dimer level was determined in 24 of the patients and in 29 of the healthy controls, levels of fibrinogen in 27 of the patients and in 29 of the healthy controls, and levels of vWF in 27 of the patients vs 29 of the healthy controls. There was a marked difference of D-dimer levels between groups (Table 1). When subgroups according to PASP levels were analyzed, the mean D-dimer value in the group with normal PASP was 287.92 (614.92) ng/mL (n=39; 30 controls and 9 cases); in the borderline group, 985.04 (1660.38) ng/mL (n=18; 2 controls and 16 cases); and in the group with pathological PASP level, 978.98 (614.99) ng/mL (n=7, all cases) (Figure 4). There were differences between the group with normal PASP levels and the group with pathological PASP levels (\( P = .001 \)) and also between the group with normal PASP levels and the group with borderline PASP levels (\( P = .005 \)). Over-all, there was a high positive correlation between D-dimer and PASP (\( r = 0.52; P < .001 \)). There were significant differences in the mean (SD) vWF in plasma between controls (92.69% [28.92%]) and patients (124.41% [52.28%]; \( P = .01 \)). There were no differences in levels of vWF between patients with KTS and those in the venous malformation group (\( P = .27 \)). There was a moderate positive correlation between levels of vWF and levels of PASP (\( r = 0.42; P < .001 \)). There was no significant difference in levels of fibrinogen between patients (260.81 [84.62] mg/dL) and healthy controls (257.93 [51.32] mg/dL; \( P = .55 \)). (To convert fibrinogen to micromoles per liter, multiply by 0.0294.) The PASP levels of patients with KTS or extensive venous malformations did not correlate with the levels of D-dimer, vWF, and fibrinogen.

This study shows statistically significant differences in the values of PASP in patients with extensive venous malformations and also in patients with KTS compared with the respective healthy control populations. It has previously been suggested that recurrent or unresolved pulmonary embolisms from the vascular malformation due to hypercoagulability can lead to the development of CTEPH in patients with KTS and pure extensive venous malformations. CTEPH results from incomplete resolution of the vascular obstruction caused by pulmonary embolism. Pulmonary hemodynamic progression is thought to be the consequence of the development of a secondary arteriopathy in nonobstructed precapillary pulmonary vessels. Pulmonary small vascular malformations are thought to play an important role in other pulmonary vascular disorders such as veno-occlusive disease and pulmonary capillary hemangiomatosis. It was not confirmed in these patients if the cause of the high values of PASP observed was due to CTEPH.

Coagulation disorders (LIC) have been reported in patients with venous malformations of the limbs and trunk, mainly with elevations in D-dimer levels. D-dimer, a split product of fibrin degradation by plasmin, has been used as a marker for various diseases. LIC is frequently associated with venous malformations, and

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**Table 1. Data of Patients and Controls**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=32)</th>
<th>Controls (n=32)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
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<td>Male</td>
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<td>17</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>27 (14)</td>
<td>31 (13)</td>
<td>.30</td>
</tr>
<tr>
<td>PASP level, mm Hg</td>
<td>42.16 (8.49)</td>
<td>27.69 (6.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fibrinogen level, mg/dL</td>
<td>260.81 (84.62)</td>
<td>257.93 (51.32)</td>
<td>.55</td>
</tr>
<tr>
<td>vWF, %</td>
<td>124.41 (52.28)</td>
<td>92.69 (28.92)</td>
<td>.01</td>
</tr>
<tr>
<td>D-dimer level, ng/mL</td>
<td>1032.99 (1367.0)</td>
<td>102.97 (29.39)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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**COMMENT**

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large surface area and muscle involvement are strong predictive criteria for higher levels of D-dimers. This could explain why the patients included in this study with large and deep venous malformations have higher levels of D-dimers than patients with KTS. It has been reported that in patients with idiopathic PAH, mean D-dimer levels were significantly higher than in the matched control group. There is also evidence to suggest that D-dimer levels in patients with idiopathic PAH are associated with disease severity and prognosis. Elevated levels of D-dimer have also been found in secondary PAH. To our knowledge, we show for the first time that levels of D-dimer in plasma are highly correlated with PASP values in patients with slow-flow vascular malformations.

This study also detected a moderately positive correlation between PASP and vWF, which to our knowledge has not been previously described in patients with vascular malformations. Von Willebrand factor is a large multimeric glycoprotein present in blood plasma and is produced constitutively in the endothelium. It is a marker of endothelium dysfunction. In pathological conditions, endothelial cell stimulation is followed by rapid release of vWF from Weibel-Palade bodies and plasma vWF levels increase. If endothelial cell function is restored, vWF: Ag levels return to normal. Von Willebrand factor independently predicts long-term survival in patients with PAH. Also, in secondary pulmonary hypertension, it has been demonstrated that levels of vWF are higher in patients than in controls. Although the common pathogenic mechanisms of PAH are not known, pulmonary vascular changes of distinctive causes lead to endothelial dysfunction and activation of a cascade of different regulatory systems (coagulatory, inflammatory, and

Table 2. Patient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>VM (n=14)</th>
<th>KTS (n=18)</th>
<th>P Value</th>
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</thead>
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<td>11</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>21.6 (12.3)</td>
<td>30.4 (15.1)</td>
<td>.09</td>
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<td>Location, No. of malformations</td>
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<tr>
<td>Lower extremity</td>
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<td>Upper extremity</td>
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</tr>
<tr>
<td>Trunk</td>
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<td></td>
<td></td>
</tr>
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<td>Head and neck</td>
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<td></td>
</tr>
<tr>
<td>Hemicorporal</td>
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<td>2</td>
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</tr>
<tr>
<td>Multiples sites</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PASP level, mean (SD), mm Hg</td>
<td>41.71 (8.54)</td>
<td>42.50 (8.67)</td>
<td>.80</td>
</tr>
<tr>
<td>Fibrinogen level, mean (SD), mg/dL</td>
<td>228.55 (57.18)</td>
<td>283.0 (94.58)</td>
<td>.08</td>
</tr>
<tr>
<td>vWF, mean No. (%)</td>
<td>112.0 (45.93)</td>
<td>132.94 (56.05)</td>
<td>.27</td>
</tr>
<tr>
<td>D-dimer level, mean (SD), ng/mL</td>
<td>2316.16 (1724.80)</td>
<td>391.40 (399.74)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: KTS, Klippel-Trenaunay syndrome; NA, not applicable; PASP, pulmonary artery systolic pressure; VM, venous malformation; vWF, von Willebrand factor.

SI conversion factor: To convert fibrinogen to micromoles per liter, multiply by 0.0294.

a In 1 patient, the VM affected both legs.

b The malformation in 2 patients with KTS affected both legs.

Figure 3. Pulmonary artery systolic pressure in healthy controls and patients. The bottom and top of the boxes are the 25th and 75th percentiles (the lower and upper quartiles, respectively), and the bands near the middle of the boxes are the 50th percentile (median).

Figure 4. D-dimer levels according the value of pulmonary artery systolic pressure (PASP). The bottom and top of the boxes are the 25th and 75th percentiles (the lower and upper quartiles, respectively), and the bands near the middle of the box are the 50th percentile (median). The asterisks indicate outliers.
PAH is a serious process that leads to right ventricular insufficiency and can cause death. Most patients are diagnosed in advanced phases when they already have symptoms. Based on these results, an echocardiogram should be performed in all patients diagnosed as having an extensive slow-flow vascular malformation, although such a measure may not be necessary in those with medium or small malformations (Figure 5). Altered PASP values may exist in children with extensive slow-flow vascular malformations; therefore, there is no justification for waiting until the patient is an adult to perform an echocardiogram. Furthermore, the echocardiogram is a painless and innocuous test and can be easily performed in children. More extensive studies are needed to confirm the high prevalence of PAH in asymptomatic patients with slow-flow vascular malformations and to determine who should be referred for a baseline cardiac study to exclude the presence of PAH.

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Correspondence: Pedro Redondo, MD, PhD, Department of Dermatology, University Clinic of Navarra, 31008 Pamplona, Spain (predondo@unav.es).
Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Rodriguez-Manero and Aguado contributed equally to this work and both should be considered first authors. Study concept and design: Rodriguez-Manero, Aguado, and Redondo. Acquisition of data: Rodriguez-Manero, Aguado, and Redondo. Analysis and interpretation of data: Rodriguez-Manero and Aguado. Drafting of the manuscript: Rodriguez-Manero, Aguado, and Redondo. Critical revision of the manuscript for important intellectual content: Rodriguez-Manero, Aguado, and Redondo. Statistical analysis: Rodriguez-Manero, Aguado, and Redondo.
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